THE PHARMACOKINETICS AND TOXICITY OF ANTITUBERCULOSIS AGENTS AND OTHER CO-ADMINISTERED DRUGS IN CHILDREN WITH TUBERCULOSIS, WITH AND WITHOUT HIV INFECTION, AND THEIR RELATIONSHIP TO NUTRITIONAL STATUS

by
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Thesis presented in partial fulfilment of the requirements for the degree Master of Nutrition at the University of Stellenbosch

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DECLARATION

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ABSTRACT

Problem definition: Malnutrition increases the incidence and exacerbates the clinical manifestations of TB. Hepatotoxicity is one of the most serious and most frequent side-effects of anti-tuberculosis drugs and may be three times higher in malnourished patients.

Objective: The influence of nutritional and retroviral status on the bio-availability and toxicity of anti-tuberculosis agents was studied and a possible relationship between abdominal lymph node enlargement and the occurrence of malnutrition investigated.

Subjects and setting: The study subjects were 53 children, 19 HIV-infected and 34 HIV-uninfected, aged 3 months to 13 years with probable or confirmed tuberculosis admitted to the paediatric ward of Brooklyn Hospital for Chest Diseases in Cape Town, South Africa. The nutritional status of the children was assessed over the first four months of tuberculosis treatment by nutrient intake, anthropometric status and biochemical parameters. The relationship between abdominal lymph node enlargement and the occurrence of malnutrition was also evaluated. Pharmacokinetic studies were performed to evaluate the bio-availability of anti-tuberculosis agents and drug hepato-toxicity was evaluated by liver function.

Results: Stunting (46.27%) and underweight (34.51%) were the most common types of malnutrition in the children studied. HIV-infection did not have a significant effect on stunting or wasting, but had a significant effect (p=0.003) on underweight for age with 31.5% HIV-infected compared to 2.9% HIV-uninfected at enrolment, but the effect was not statistically significant at month 4. There was no change in the number of stunted, wasted or underweight children from enrolment after 1 month of treatment to month 4 of treatment.

HIV-infection did not have a significant effect on abdominal TB involvement (p=0.43354), and nutritional status was not significantly affected by abdominal lymph-node involvement.

At enrolment weight for age had a significant effect on AST and ALT with p-values of 0.02166 and 0.02765 respectively and wasting had a significant effect on GGT at enrolment (p=0.03014). However on enrolment only two HIV-infected and two HIV-uninfected children had ALT values

increased >X2 normal. Similarly AST values >X3 normal were found in only one HIV-infected child and two HIV-uninfected children. Stunting did not significantly affect liver enzymes. Anthopometric status did not have a significant effect on liver enzymes at month 4.

None of the parameters used to determine nutritional status had a statistically significant effect on INH-levels or RMP-levels.

HIV-infection had a significant negatve effect on selenium (p=0.030 and 0.012) and ferritin (p=0.026 and 0.002) at enrolment and month 4 and on IBC (p=0.025) at enrolment. At month 4 HIV-infection had a significant negative effect on the mean vitamin C-levels (p=0.005).

Conclusions: HIV co-infection did not affect the extent or distribution of body composition changes in this study. Stunting was the most prevalent form of malnutrition in the study group, indicating longstanding undernutrition, which may be due to factors other than the present TB infection. Appropriate treatment of tuberculosis did not appear to affect the nutritional status over the four month period of the study.

OPSOMMING

Probleemstelling: Wanvoeding verhoog die insidensie en vererger die kliniese beeld van TB. Hepatotoksisiteit is een van die ernstigste en algemeenste newe-effekte van anti-tuberkulose middels en mag tot drie keer hoër wees in wangevoede pasiënte.

Doelwit: Die invloed van die kinders se voedings- en retrovirale status op die bio-beskikbaarheid en toksisiteit van anti-tuberkulose middels was ondersoek en ‘n moontlike verband tussen vergrote abdominale limfnodes en die voorkoms van wanvoeding was ondersoek.

Deelnemers en omgewing: Die deelnemers aan die studie was 53 kinders, 19 HIV-positief en 34 HIV-negatief, tussen die ouderdomme van 3 maande en 13 jaar met moontlike of bevestigde tuberkulose toegelaat tot die pediatriese saal van Brooklyn Hospitaal vir Borskwale in Kaapstad, Suid Afrika. Die voedingstatus van die kinders was bepaal oor die eerste vier maande van tuberkulose behandeling ten opsigte van nutriëntinname, antropometriese status en biochemiese parameters. Die verhouding tussen vergrootte abdominale limfnodes en die voorkoms van wanvoeding was ook geëvalueer. Farmakokinetiese studies was uitgevoer om die bio-beskikbaarheid van anti-tuberkulose middels te evalueer en hepatotoksisiteit was deur lewerfunksie geëvalueer.

Resultate: Dwerggroei (46.27%) en ondergewig (34.51%) was die algemeenste tipes wanvoeding teenwoordig by die kinders bestudeer. HIV-infeksie het nie ‘n noemenswaardige effek op dwerggroei of uittering gehad nie, maar het wel ‘n noemenswaardige effek (p=0.003) getoon op ondergewig vir ouderdom met 31.5% HIV-positief vergeleke met 2.9% HIV-negatief by inskrywing, wat nie statisties noemenswaardig was teen maand 4 nie. Daar was geen verandering in die hoeveelheid kinders met dwerggroei, uittering of ondergewig vanaf inskrywing na 1 maand van behandeling tot maand 4 van behandeling nie.

HIV-infeksie het nie 'n noemenswaardige effek op abdominale TB gehad nie (p=0.43354), en vergrootte abdominale limfnodes het nie ‘n noemenswaardige effek op voedingstatus gehad nie.

By inskrywing het gewig vir ouderdom ‘n noemenswaardige effek op AST en ALT gehad met p-waardes van 0.02166 en 0.02765 onderskeidelik en uittering het ‘n noemenswaardige effek op GGT by inskrywing gehad (p=0.03014). Dwerggroei het nie die lewerensieme noemenswaardig beïnvloed nie. Antropometriese status het nie ‘n noemenswaardige effek op lewerensieme teen maand 4 gehad nie.

Geen van die parameters wat gebruik is om voedingstatus te bepaal het ‘n noemenswaardige statistiese effek op INH-vlakke of RMP-vlakke gehad nie.

HIV-infeksie het ‘n noemenswaardige effek op selenium (p=0.030 en 0.012) en ferritien (p=0.026 en 0.002) by inskrywing en maand 4 gehad en op IBC (p=0.025) by inskrywing. HIV-infeksie het ‘n statisties noemenswaardige effek op die gemiddelde vitamien C-vlakke (p=0.005).

Gevolgtrekking: HIV ko-infeksie het nie die verspreiding of mate van liggaamsamestelling veranderinge in hierdie studie geaffekteer nie. Dwerggroei was die algemeenste vorm van wanvoeding in die studiegroep, wat langstaande wanvoeding aandui en toegeskryf mag word aan faktore buiten die huidige TB infeksie. Toepaslike tuberkulose behandeling het nie ‘n wesenlike effek op voedingstatus gehad tydens die vier maande periode van die studie nie.

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LIST OF ABBREVIATIONS

AIDS:	Acquired immuno-deficiency syndrome
AMA:	Arm muscle area
ART:	Anti-retroviral treatment
BMI:	Body mass index
BHCD:	Brooklyn Hospital for Chest Diseases
Cyp2E1:	Cytochrome P450 2E1
CDC:	Centre for Disease Control
DOTS:	Directly observed therapy
ELIZA:	Enzyme linked immunosorbent assay
FBC:	Full blood count
FFQ:	Food frequency questionnaire
GST:	Glutathione-s transferase
H/A:	Height for age
HIV:	Human immuno-deficiency virus
IFCC:	International federation of clinical chemistry and laboratory medicine
INH:	Isoniazid
IgA:	Immunoglobulin A
Ml:	Millileter
MO:	Medical officer
MUAC:	Mid upper arm circumference
NAT 2:	N-acetyltransferase
NCHS:	National Centre for Health Statistics
Neg:	Negative
PEM:	Protein energy malnutrition

Pos:	Positive
PZA:	Pyrazinamide
RDA:	Recommended dietary allowance
RMP:	Rifampicin
SD:	Standard deviation
SSF:	Subscapular skinfold
TB:	Tuberculosis
TBM:	TB meningitis
TSF:	Triceps skinfold
WHO:	World Health Organisation
W/H:	Weight for height
W/A:	Weight for age

CHAPTER 1: INTRODUCTION AND MOTIVATION OF THE STUDY

1.1 Introduction

Tuberculosis (TB) is the most common cause of infection-related deaths worldwide and is the most common opportunistic infection to develop in human immunodeficiency virus (HIV)-infected children and adults. This interaction has a negative effect on the prognosis of both diseases and has been called the "cursed duet".[1]

Africa, home to 11% of the world's population, has 29% of the global number of TB cases. The World Health Organisation (WHO) estimates that the incidence of TB in Africa more than doubled between 1990 and 2006, from 149 to 334 per 100 000 population per year in contrast with the stable or declining rates in all other regions during this period.[2,3] HIV/AIDS is responsible for most of the recent increase in TB incidence in Africa. Co-infection with HIV greatly increases the risk of latent TB will develop into active disease.[2,4] Table 1.1 shows the estimated prevalence and incidence of TB globally and compared to South Africa. From these figures it is clear why TB has been called a time-bomb in Africa.[5]

Table 1.1 Estimated global TB cases

	Global	South Africa	SA ranking world wide
TB prevalence rate (people living with TB) per 100 000 population	219	998	Third highest
New TB cases per 100 000 population	139	940	Second highest
TB in HIV positive people per 100 000 population	11	416	Second highest
HIV prevalence in incident TB cases	8%	44%	Sixth highest

Source: Data from Global Health Facts[6]

Risk factors for the development of active TB disease include HIV-infection, sharing a home with someone who has active TB, malnutrition, poverty and impaired immune function.[4] Children are usually infected with TB by a smear-positive family member or other close contact. Therefore, the most effective way to prevent childhood TB is early identification and proper treatment of infectious adult cases.[3] Children may present with active TB at any age, but disease is most common between one and four years, most probably due to an underdeveloped immune response.[7] Although the short-term response to treatment in HIV-infected and non-HIV-infected TB patients is usually considered similar, the mortality during therapy is considerably higher in both children[8,9,10] and adults who are HIV-infected.[11,12,13]

HIV-infection impairs cell-mediated immunity, increasing the risk of TB infection and the reactivation of latent TB in adults and children.[3] The development of active TB disease is the first sign of AIDS in many HIV-infected individuals. Active TB disease often occurs at higher CD4 lymphocyte counts than other HIV-related illnesses. Active TB often decreases the number of CD4 lymphocytes which increases HIV viral replication. Both diseases therefore accelerate the progress of the other.[2,7]

The latest UNAIDS data shows global HIV prevalence has leveled off and that the number of new infections have been reduced, in part as a result of the impact of HIV programs. Nonetheless, in 2007 33.2 million people were estimated to be living with HIV, of which 2 million are children under 15 years of age. In the same year 2.7 million people became newly infected, including 370 000 children under the age of 15 years and 2 million people (270 000 children) died of acquired immunodeficiency syndrome (AIDS).[14]

Southern Africa carries a disproportionate share of the global burden of HIV, 35% of new HIV infections and 38% of AIDS deaths in 2007. Sub-Saharan Africa remains the most severely affected as 68% of the global total and almost 90% of infected children live in Sub-Saharan Africa. In Table 1.2 the prevalence of HIV-infection in South Africa is compared with global rates.[14]

Table 1.2 Estimated HIV-infection rates (2007)

	Global	Sub-Saharan Africa	South Africa
Estimated number of people (all ages) living with HIV	33 million (30 – 36 million)	22 million (20.5 – 23.6 million)	5.7 million (4.9 – 6.6 million)
Estimated number of children (0-14 years) living with HIV	2 million	1.8 million	280 000
Estimated adult (15-49 years) HIV prevalence rate	0.8%	5%	18.1%
Children (0-17 years) orphaned by AIDS	15 million	11.6 million	1.4 million

Source: Data from UNAIDS[14]

World-wide approximately one third of people living with HIV are co-infected with TB[1], while 50% of all HIV-infected patients in South Africa have TB.[15] TB kills more HIV-infected people in Africa than any other AIDS-related disease. Among HIV-infected children, TB accounts for up to one in five of all deaths.[15]

Malnutrition raises the incidence and exacerbates the clinical manifestations of TB.[16] Nutritional status is one of the most important determinants of resistance to infection.[2,17,18,19] Undernutrition is implicated in up to 50% of all deaths in children under 5. Table 1.3 shows the percentage of malnourished children younger than 5 years of age, globally and in South Africa. The South African numbers are estimated by UNICEF and might not be a true reflection of the extent of malnutrition in South Africa.[20]

Table 1.3 Percentage of under-fives malnourished (2000-2006)

		Global	Sub-Saharan Africa	South Africa
Underweight (NCHS/WHO)	Moderate and severe	25	28	12
	Severe	-	8	2
Wasted (NCHS/WHO)	Moderate and severe	11	9	3
Stunted (NCHS/WHO)	Moderate and severe	28	38	25

Source: Data from UNICEF[20]

1.2 Nutritional Status and Immunity

The human body (host) has an ability to distinguish between self and non-self substances or organisms. Working together, a multi-level system of cells and biochemical factors recognize, attack and destroy the foreign substance. Components of immune responses may be categorised as non-specific and specific responses, as illustrated in Figure 1.1.[21,22]

Antigen non-specific responses do not require recognition of a particular antigen and include the mucous membrane and phagocytes. The mucous secretions of the mucous membrane contain a variety of biochemical and immunological factors that attack bacterial cell walls, starting the process leading to the destruction of bacteria. Phagocytes (granulocytes and macrophages) move to the area of foreign invasion and participate directly in intracellular killing of bacteria and viruses. Macrophages and their secretory products directly and indirectly stimulate components of the immune response, as well as B- and T-cell functions. Part of the stimulation process is the production of lymphokines, e.g. interferons and interleukin-1. Interferons stimulate cell replication and differentiation and are active in stimulating T-cell functions. Interleukin-1 stimulates the hypothalamus to induce fever and heighten the rate of body metabolism to fight infection.[21,22,23]

An antigen specific response requires the recognition of foreign antigens, is specific in its interaction with the antigen and has memory of past antigenic exposure. Antigen specific responses include antibodies and cell-mediated immunity. Antibodies are immunoglobulins produced by mature B-lymphocytes. Large amounts of antibodies are produced to complex specifically with the antigen. Cell-mediated immunity consists of T-lymphocytes. The antigen is attacked for direct killing of the invading organism. Activation of antigen specific complement promotes phacocytosis, viral neutralization and lysis of virus infected cells after bacterial removal.[7,21,22,23]

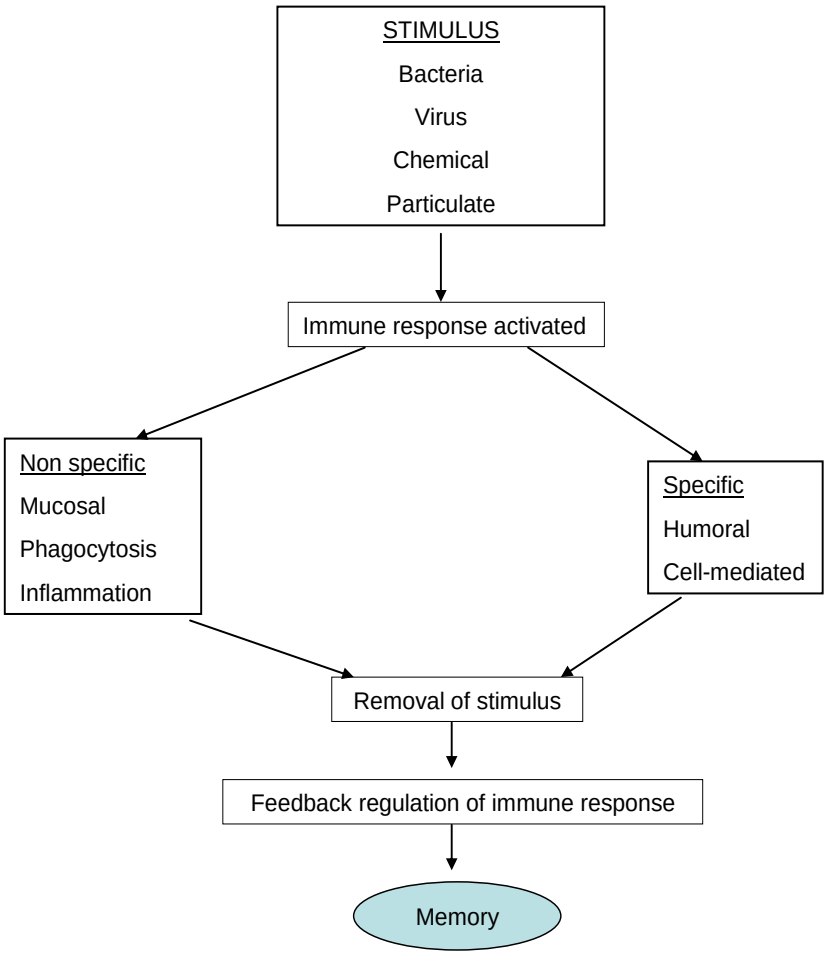

Figure 1.1: The specific and non-specific components of the immune response

Malnutrition limits cell-mediated and humoral immunity and increases susceptibility to infection.[24,25] Infection can lead to nutritional stress and weight loss, resulting in a weakened immune function and nutritional status.[7]

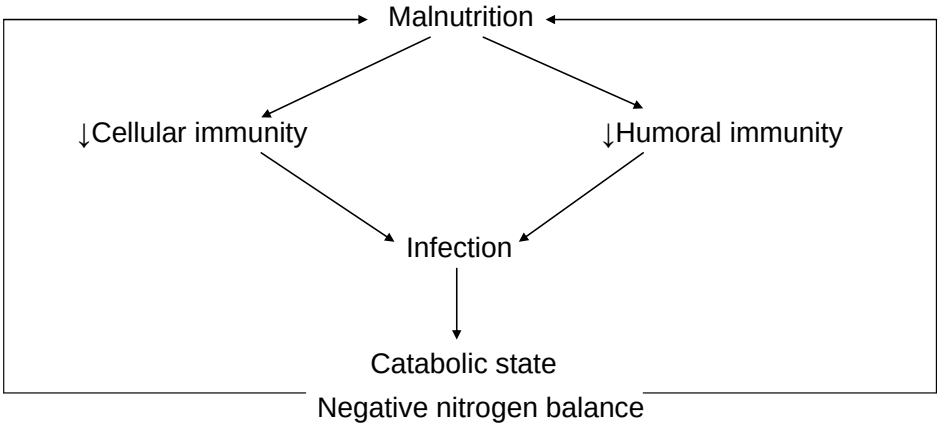

Figure 1.2: The malnutrition-infection cycle

The immune response is a rapidly acting system with cells and secretory products having relatively short life spans, therefore nutrient functions have dramatic effects on the responsiveness of the system. The severity of the impairment of immunity depends upon the severity of nutrient deficiency. (Figure 1.2) Isolated deficiencies are rare, with the exception of iron, vitamin A and zinc, but they frequently complicate malnutrition.[7,23]

Nutrients are involved in different ways in the immune response, including the anatomical development of lymphoid tissue, mucous production, synthesis of immunologically active proteins, cell proliferation and regulation of immune processes.[26] Table 1.4 summarises the nutrients involved in different immune functions.

Table 1.4: Nutrients affecting immune function

Immune function	Nutrients involved
Non specific immune response	
Mucosal ▪ Lysozymes	Protein-energy malnutrition (PEM) Vitamin A
Phagocytes ▪ Macrophages ▪ Granulocytes	Iron deficiency Vitamin C Fatty acids
Specific immune response	
Humoral ▪ B-lymphocytes	 Iron Vitamin A Vitamin E Vitamin B6 Essential fatty acids
Cell mediated ▪ T-lymphocytes	 Vitamin A Vitamin B12 Zinc Folic acid Poly unsaturated fatty acids

In protein energy malnutrition in children the thymus becomes atrophied resulting in decreased T-lymphocytes in circulation. The total number of circulating B-cells and serum immunoglobulin concentrations are also reduced. Total energy restriction alone does not seem to be nearly as devastating to t-cell functions as protein deficiency. A delayed chemotaxic movement of

neutrophils toward the stimulus and defective microbicidal activity and impaired release of lysosomal enzymes is also seen in malnutrition.[26,27]

The interrelationship between infection, nutritional status and immune function are especially apparent in individuals with HIV, who have impaired immune function and altered nutritional status.[23,24,28] Immune defence at the epithelial barrier of the undernourished host is impaired due to altered structure of the gut mucosa, such as flattened hypotrophic microvilli, reduced lymphocyte counts in Peyer's patches, and reduced immunoglobulin A (IgA) secretion. Malnutrition reduces the availability of complement components, thereby affecting the capacity of phagocytes to eliminate pathogens.[21,24,26]

1.3 Effect of Malnutrition on TB and HIV

TB infection occurs when individuals inhale the aerosolized tubercle bacilli. Alveolar macrophages phagocytose the inhaled bacilli. The macrophages are unable to kill the mycobacteria and the bacilli continue to multiply. A cell-mediated response terminates the growth of *Mycobacteria tuberculosis* 2-3 weeks after infection. However, the initial pulmonary site of infection (the primary focus or Ghon focus) and its adjacent lymph nodes (together the primary complex or Ghon complex) sometimes enlarge and develop necrosis and calcification.

Malnutrition is an important risk factor for TB, because cell-mediated immunity is the main host defense against TB.[29,30] Individuals with immuno-suppression or malnutrition have a greater risk of TB, since infection is more likely to progress to active TB when the cell mediated immune-response is impaired, as observed in people with HIV infection.[31] The HIV epidemic continues to have a major impact on child health and survival worldwide. Seventy five percent of all infected children die before the age of five years.[14]

Body weight consists of fat free mass (muscle tissue) and fat mass. Patients with active TB generally have lower body mass index (BMI), skinfold thicknesses, mid-upper arm circumference (MUAC) and proportion of fat than healthy adults.[32] Wasting in TB is associated with overall depletion of lean and fat tissue in approximately equal proportions, but lean tissue depletion is greater in the limbs and fat tissue depletion greater in the trunk in adults.[32,33] HIV co-infection

does not affect the extent or distribution of the body composition changes[33], suggesting that TB (rather than HIV) is the dominant factor driving the wasting in patients with co-infection. Published data of anthropometric studies in children with TB and HIV and the response to treatment are scarce, rather focusing on adults with co-infection.

Weight loss and malnutrition frequently occurs in the later stages of HIV-infection and both patients with AIDS and protein energy malnutrition (PEM) will experience infections of mycotic, parasitic and bacterial origin.[34] Nutritional complications develop as the disease progresses and signs and symptoms of HIV-infection manifest. Malabsorption and diarrhea are the most important nutritional problems encountered in advanced AIDS[35,36] and are caused by a relatively high cell turnover rate of the mucosal tissue of the gastrointestinal tract.[37] This impairs the absorption of several essential nutrients and promotes intestinal infections and diarrhoea.[35,38] Patients with intestinal infection of the small bowel commonly have malabsorption of fat, mono- and disaccharides, nitrogen, vitamin B_{12}, folate, minerals and trace elements.[39] Fat malabsorption frequently occurs in AIDS patients and is not always accompanied by diarrhoea.

Severe weight loss as seen in PEM may cause organ damage, which increases the risk of a fatal outcome from infections.[1,40] Myocardial cells in the heart show histological changes and the cardiac reserve decreases, atrophy of the digestive system and bacterial overgrowth is common. The exocrine function of the pancreas is impaired and fatty infiltration of the liver takes place. Brain atrophy, causing intellectual and emotional disturbances may also occur.[21] Body cell mass, the amount of functional protoplasm in non-adipose tissue, may be the best predictor of death.[41] Metabolic (endocrine) abnormalities common in PEM, such as decreased levels of insulin and somatomedines causes a slowing down of growth and decreased levels of cortisol triggers an increased amino-acid release. This contributes to the depletion of lean tissue with little loss of fat[36,42], in contrast with starvation, where fat stores are depleted.[40]

1.4 Micronutrient Malnutrition

Micronutrients are important for the functioning of the immune response. Vitamin A is needed for the maintenance of healthy epithelial tissue (mucosal immunity) and antibody production (humoral immunity).[43] The active metabolite of vitamin D, calcitriol, has an effect on the synthesis of immunoregulatory molecules, namely macrophages and lymphocytes.[44] Iron

deficiency causes a reduction in interleukin-1 production (phagocytosis). On the other hand iron is needed by most bacteria for growth and multiplication. Clinical data does not support the suggestion that iron deficiency protects against infection.[45] Vitamin C plays a role in the mobilization and aggregation of macrophages. Low levels of vitamin B_{12}, zinc vitamin A and folic acid result in impaired T-cell proliferative responsiveness.[46]

Micronutrient deficiencies have been described in individuals with HIV infection[47] and in those with TB[32,48], resulting from poor nutrition as well as the diseases itself. It has been found that patients with tuberculosis, as well as patients with HIV are prone to developing deficiencies of vitamin A, vitamin B_6, folate, vitamin C, vitamin E, zinc, selenium and thiamin.[45,49,50] Deficiencies of vitamin B_{12} and vitamin C are also more prevalent among HIV-infected adults than in HIV-uninfected adults.[50]

Although zinc plays a fundamental role in immunity, the safety of zinc supplementation in HIV-infected adults is controversial, as higher dietary intake of zinc appear to be related to decreased survival.[45]

1.5 Metabolism and Toxicity of Antituberculosis Agents

For drugs to have the intended disease altering effect, they have to go through several phases. First is the pharmacokinetics, that is the movement of the agent. After the administration absorption, distribution, metabolism and excretion takes place. Part two is the pharmacodynamic (the action of the drug) part. This includes binding to receptors, inhibiting enzymes or changing of cell membrane function.

There are a number of pharmacokinetic aberrations in malnutrition which are related to hepatic and renal dysfunction and changes in plasma protein binding. The liver is the main drug metabolizing organ and is anatomically and functionally deranged in PEM.[51,52]

Drugs are bound to plasma proteins to be distributed through the body. This binding is reversible and only free agent can move over capillary membranes. It has been found that an altered serum protein pattern (decreased albumin, increased total protein) in often seen in AIDS

patients.[53] As rifampicin is relatively highly protein –bound (up to 80%)[54] this altered protein pattern may affect rifampicin to a larger extent than isoniazid or pyrazinamide.[53] If plasma protein binding is decreased the free drug concentration is increased. The therapeutic effect may not be enhanced since, being free, the drug may be eliminated more rapidly.[55]

In patients co-infected with HIV and TB altered pharmacokinetic profiles for anti-mycobacterial drugs are described.[56] AIDS may predispose patients to malabsorption of antimycobacterial drugs due to its gastrointestinal associations such as opportunistic bowel infections, gastric hypoacidity and enteropathy, thus affecting the efficacy of treatment.[57]

Isoniazid (INH), rifampicin (RMP) and pyrazinamide (PZA) are the three main drugs used to treat tuberculosis.[58] Hepatotoxicity is one of the most serious and most frequent side-effects of these drugs. The severity ranges from alteration in liver enzymes, chronic active hepatitis and acute hepatitis, occasionally complicated by acute liver failure with high mortality unless transplanted.[59]

The most widely accepted risk factors for hepatotoxocity in patients treated with anitituberculosis drugs are old age, previous history of chronic liver disease, chronic alcoholism, elevated serum transaminases prior to treatment, concomitant use of certain other drugs and poor nutritional status.[60] Anti-tuberculosis therapy inducible cytochrome P-450 2 E1 (cyp2E1) is expressed in the liver. Recent studies[61,62] have shown that polymorphism of the N-acetyltranferase2 (NAT2) genes and glutathione-s transferases (GST) are the main susceptibility risk factors for anti-tuberculosis therapy induced hepatotoxicity.[61] Antituberculosis therapy induced hepatotoxicity in malnutrition may be explained by a depletion of glutathione stores, which results in increased vulnerability to oxidative injuries.[62] It has been shown that the incidence of antituberculosis therapy induced hepatotoxicity may be three times higher in malnourished patients.[63]

Peripheral neuropathy is a known adverse effect associated with antituberculosis therapy. INH causes sensory and motor neuropathy, with an estimated incidence of 0.2%, although at higher doses the incidence has been reported to be as high as 40%.[64,65] Old age, alcoholism, malnutrition, pregnancy, as well as renal or hepatic dysfunction are risk factors for the development of INH-associated neuropathy.[66] Co-administration of pyridoxine is protective, although excessive amounts may cause peripheral neuropathy.[67]

1.6 Bio-availability of Anti-tuberculosis Agents

Bio-availability measures the relative amount of an administered drug in the circulation (Cp), against a standard reference over time. Parameters include the time needed to reach maximum serum concentration (t max) and maximum concentration for a given dose (C max).[53,68] It has been found that HIV-infection causes malabsorption of first line anti-TB drugs even at an early stage of the disease. HIV-infected persons have increased intestinal permeability and a significant correlation exists between malabsorption and degree of immunosuppression.[52,69]

RMP INH and PZAare absorbed from the proximal gastro-intestinal tract. Although malabsorption is common in patients with intestinal TB it does not impair blood levels of these drugs.[70]

The metabolizing enzyme of INH is a hepatic N-acetyl transferase, which displayes genetic polymorphism. This enzyme has two phenotypes, slow and rapid acetylators of INH. The rapid acetylators have four to five times more of the enzyme than slow acetylators. Rapid acetylators therefore have enhanced metabolism of INH causing lower blood levels and urinary excretion than slow acetylators.[69]

1.7 Abdominal Lymph Node Involvement

A significant number of children with TB will also have involvement of the abdominal lymphnodes. The lymphatic drainage of the intestinal tract may be compromised due to obstruction, which leads to bacterial overgrowth in the gut, a variant of stagnant loop syndrome. This contributes to the development of malnutrition by malabsorption and loss of nutrients. In the small intestine the ileum is more commonly involved than the jejunum. This is attributed to the abundance of lymphoid tissue (Peyer patches) in the distal and terminal ileum.[71] The result will be sub-optimal absorption of fat, fat-soluble vitamins, protein, carbohydrate, electrolytes and minerals.[72]

1.8 Motivation for the Study

Limited information is available describing the pharmacokinetics of anti-TB drugs in children and the possible influence of HIV infection and nutritional status thereupon, although it is well described in adult TB patients.

This study is nested in a primary study, sponsored by Bristol-Myers Squibb (BMS), examining the duration of treatment for TB and the pharmacokinetics and toxicity of anti-TB agents and other co-administered drugs in children, with and without HIV-infection and the relationship to the the NAT2 acetylator genotype and phenotype.

The nutritional status of a group of children admitted to a TB referral hospital with severe forms of childhood TB is described. The influence of the children's nutritional status on the absorption, metabolism and toxicity of anti-TB agents was examined. The relationship between abdominal lymph node enlargement and the occurrence of malnutrition was also evaluated.

CHAPTER 2: METHODOLOGY

2.1 Aim

The aim of the study was to evaluate the influence of nutritional status of children aged 3 months to 13 years who were infected with TB, with or without HIV on the pharmacologic action and bio-availibility of anti-TB agents.

2.2 Objectives

The specific objectives were to:

1. Evaluate the nutritional status of the subjects at enrolment, and compare their anthropometric status at enrolment with anthropometric status after 4 months of anti-TB treatment and receiving a balanced diet in the hospital setting

2. Investigate the influence of the children's anthropologic status, on the absorption, metabolism, bio-availability and toxicity of anti-TB agents

3. Determine whether there was a relationship between abdominal lymph node enlargement and the occurrence of malnutrition

2.3 Study Design

The study used a prospective cohort design with a descriptive and analytical component. Convenience sampling was employed by selecting consecutive patients meeting the inclusion criteria on referral to Brooklyn Hospital for Chest Diseases (BHCD).

2.3.1 Inclusion criteria

The inclusion criteria were:

- Children between the ages of 3 months and thirteen years
- Children with probable or confirmed tuberculosis admitted to BHCD
- Written informed consent given by a parent or legal guardian for participation in the study and for HIV testing if the child's status was not known
- Children less than one month on anti-tuberculosis treatment

2.3.2 Study site

BHCD is the non-acute TB hospital for the metropolitan area of the City of Cape Town. BHCD admits complicated cases of tuberculosis and patients who are unable to receive community treatment. Poor socio-economic status resulting in lack of transportation to clinics and inability of children's caregivers to accompany them to clinics are some of the main reasons why patients cannot receive effective community-based treatment.

BHCD has 60 children's beds and has approximately 140 paediatric admissions annually. Children enrolled in this study were drawn from those admitted to BHCD. As BHCD is not equipped for the management of more serious complications of TB or HIV/AIDS, it was necessary, at times, to transfer children to other secondary or tertiary hospitals.

2.3.3 Subjects

Of the 420 children in BHCD during the period January 2004 to December 2006 (the duration of the study), 68 children were eligible for enrolment. Consent was refused for 1 patient to be enrolled and consent could not be obtained for 7 children, because they did not have parents or legal guardians. Sixty children, 26 HIV-infected and 34 HIV-uninfected were enrolled in the study. Two groups of children were studied, the one with TB complicated by HIV/AIDS, and the other without HIV/AIDS. Four children (all HIV-infected) were transferred back to referring hospitals shortly after enrolment due to complications that could not be handled at BHCD [*Streptococcal pneumonia* infection (N=1), gastro-enteritis and dehydration due to salmonella infection (N=1) and thrombocytopenia and surgical draining of the hip (N=1)] and three children were discharged from hospital after completion of the first pharmacokinetic study. As a result these seven children were excluded from the study and their data not included in the analysis. The children were followed-up for four months.

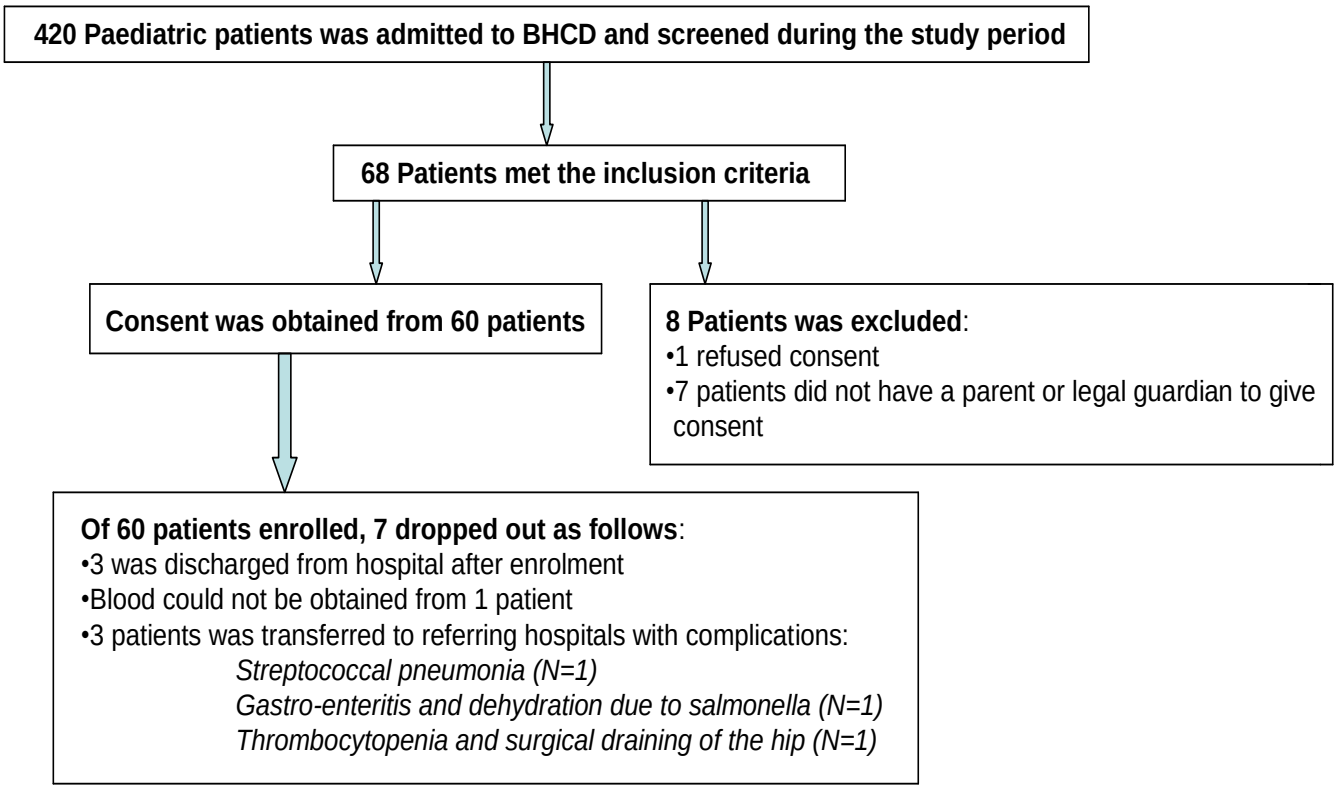

Figure 2.1: Subjects screened and enrolled in the study

2.3.4 Diagnosis of TB

A diagnosis of probable tuberculosis was made when two or more of the following clinical criteria were met:

1(a) A Mantoux test giving an induration of ≥10mm in non-HIV infected children and ≥5mm in HIV-infected children. Mantoux testing was done with tuberculin RT23 and the induration was measured in the transverse diameter of the forearm after 48-72 hours

1(b) A history of close household contact within the last year of cases with sputum microscopy smear-positive pulmonary TB

2 A chest x-ray suggestive of pulmonary TB

3 A diagnosis of tuberculous meningitis (TBM) confirmed by a cranial computerized tomogram showing hydrocephalus and basal enhancement accompanied by appropriate cerebrospinal fluid changes, or other extra-thoracic disease manifestation highly suggestive of TB

The diagnosis of tuberculosis was confirmed by a culture of *M. tuberculosis* from gastric aspirate, or sputum in older children, together with culture of cerebrospinal fluid in cases of TBM. The referring hospitals usually carried out these investigations before admission to BHCD.

2.3.5 Treatment

All forms of TB were treated with fixed dose combinations formulated for pediatric use. During the intensive phase the fixed dose combination used was Rimcure®, containing 60mg rifampin, 30mg INH and 150mg pyrazinamide. Rimactizide® containing 60mg rifampin and 30mg INH was used during the continuation phase. When the use of four drugs was advised, ethambutol was added during the intensive phase. TBM was managed with the same fixed dose combination, but with added ethionamide given for six months and using higher dosages.

All the children received a multivitamin supplement, supplying pyridoxine 0.5mg in the case of children 0-4 years of age and 1mg for those older than 5 years. Each 5ml of this supplement contained 2.300IU vitamin A, 200IU vitamin D, 1mg vitamin B1, 1.2mg Vitamin B2, 5mg nicotinamide, 35mg vitamin C and 0.0025mg viamin B12.

Highly active anti-retroviral therapy (HAART) consisted of two necleoside reverse transcriptase inhibitors and ritonavir in children under 3 years of age, and ritonavir was replaced by efavirenz in children older than 3 years.

2.3.6 Anthropometric measurements

Anthropometric measurements were taken at enrolment and monthly after the start of anti-TB treatment for four months. Data at enrolment and four months after the start of TB treatment was used to be able to make comparisons to the pharmacokinetic data. Standard NCHS/WHO procedures developed for various age groups were used to measure body weight, height and mid-upper arm circumference (MUAC).[59,60] Anthropometric measurements were taken by the researcher, a registered dietician.

2.3.6.1 Weight

The scale was calibrated to zero before weighing. Children who could not stand independently (usually those under 24 months) was weighed on an pan-type pediatric electronic scale. Infants were weighed nude and the reading taken to the nearest gram.

Children who could stand independently were weighed on a platform balance beam scale, wearing only minimum clothing (underpants). The child stood still in the middle of the platform without touching anything, while the reading was taken to the nearest 0.1kg. The reading was taken three times and an average of the three readings recorded.

2.3.6.2 Length (recumbent length)

Recumbent length was measured for infants and children younger than 24 months of age. A measuring device with a stationary headboard and movable footboard perpendicular to the backboard was used. A registered nurse assisted with the measurements.

In the supine position, the child's head was held against the backboard with the crown securely against the headboard and with the Frankfort plane perpendicular to the backboard. The child's shoulders and buttocks were securely touching the backboard while keeping the legs straight

against the backboard. The footboard was then placed against the bottom of the feet with the toes pointing upward. The measurement was read to the nearest 0.1cm. If the child could not be kept still the measurement was taken on the left leg.

2.3.6.3 Height

Children who could stand independently (older than 24 months) were measured in a standing position with a stadiometer. The child stood barefoot with head in the Frankfurt horizontal plane, feet together, knees straight, arms hanging loosely at the sides, shoulders relaxed and head, shoulder blades, buttocks and heels touching the vertical surface of the stadiometer. The headboard was lowered with enough pressure to compress the hair. The child's height was measured three times and the average of the measurements was recorded to the nearest 0.1cm.

2.3.6.4 Mid-upper arm circumference (MUAC)

The right arm of the child was measured along the horizontal line on the level of the mid-point of the upper arm. The mid-point was located by bending the right arm at a 90 degree angle, palm facing upwards and the marking the mid-point of the distance between the acromion process and the tip of the olecranon. Care was taken not to compress the soft tissue when taking the measurement with a measuring tape around the marked mid-point of the arm. Measurements was taken to the nearest millimetre.

2.3.6.5 Skinfolds

A Lange caliper was used to take measurements. The measurements were taken on the right side of the body. The site where the measurements were taken was measured and marked before a reading being taken.

The skinfold was firmly grasped by the thumb and index finger of the left hand 1cm proximal to the skin fold site and pulled away from the body. The amount of tissue grasped was enough to form a fold with parallel sides. The caliper was held in the right hand, perpendicular to the long axis of the skinfold and with the caliper's dial facing up for easy readability. The caliper tips were placed on the site, about 1cm distal to the fingers holding the skinfold, so that pressure from the

fingers would not affect the measured value. The dial was read approximately 4 seconds after the pressure from the measurer's hand has been released on the lever arm of the caliper. Two measurements were taken at each site and if they differed a third was taken. Readings were recorded to the nearest 0.5mm. Pressure was maintained with the thumb and index finger throughout each measurement.

- Triceps:

The skinfold was measured parallel with the long axis of the arm, at the mid-point between the acromion process and point of the olecranon, with the arm hanging relaxed at the child's side. The elbow was flexed 90 degrees with the palm facing upwards to determine this mid-point.

- Subscapular:

The skinfold was measured 1cm below the lowest angle of the scapula, while the child was standing. The long axis of the skinfold was on a 45 degree angle directed down and to the right side.

- Arm muscle area (AMA)

AMA is the bone-free muscle area and a good indication of lean body mass and an individual's skeletal protein reserves. It is important in growing children and valuable in evaluating possible PEM.[21] The assumption is made that triceps skinfold (TSF) and subscapular skinfold (SSF) measurements indicate energy reserves stored as fat and arm muscle area (AMA) reflect reserves stored as muscle protein. The formula used to determine AMA is:

$AMA\ (cm^2) = [MUAC-(\pi \times TSF)]^2 / 4\pi$

Values were compared with percentiles from the United States Health and Nutrition Examination Survey I.[72] Values under the 25th percentile was seen as indicative of low protein reserves.

2.3.7 Abdominal ultra-sonography

Abdominal ultrasound was done at the Department of Radiology at Tygerberg Hospital. The ultrasound was classified as normal if no enlarged lymph-nodes were found in the abdomen. Children were classified with abdominal lymph-node involvement if enlarged lymph-nodes were found in the abdomen, liver, spleen and pericardium.

2.3.8 Dietary intake

The medical officer working on the larger BMS study of which this study formed a part, obtained the informed consent and conducted the initial interview. The researcher therefore often did not have direct contact with the parent or guardian and could not conduct the 24-hour recall or food frequency questionnaire (FFQ) at the time of enrolment. The data from the subjects with whom an interview was conducted by the researcher is included in the results section. The mean intake from the FFQ and 24-hour recall was compared with the analysis of the BHCD menu. Theoretically the children would show catch-up growth if the hospital diet provide more nutrients than the regular intake as determined by the FFQ and 24-hour recall.

2.3.8.1 24-hour recall

An open-ended questionnaire based on the 24-hour recall questionnaire developed for the National Food Consumption Survey[73] was used to obtain dietary intake during a 24-hour period. The researcher asked the parent or guardian to recall all foods, beverages and snacks consumed by the child during a typical 24-hour period. Detailed descriptions of all food and beverages were recorded including portion sizes and the cooking method. Commonly eaten portion sizes in gram or ml units were included in the questionnaire. The portion sizes were estimated by using standard household utensils as well as food models from the Department of Human Nutrition of the University of Stellenbosch.[74,75]. The questionnaire was not validated before commencement of the study. Data obtained was recorded on the 24-hour recall sheet (Appendix 2).

2.3.8.2 Food frequency questionnaire

A quantitative food frequency questionnaire (Appendix 3), based on the FFQ used in for the National Food Consumption Survey[73] was used to assess food frequency over the preceding

year or the preceding six months in babies younger than one year, prior to admission to hospital. The parent or guardian was asked to recall how often food groups are consumed and the portion size of foods from the different food groups. The portion sizes were estimated using standard household utensils and selected food models.[74,75,76] The questionnaire was not validated prior to the commencement of this study. The researcher recorded the type and estimated quantity of food consumed by the child.

2.3.9 Collection of blood specimens

Blood specimens from each child were draw within one week of enrolment in the study and again four months after the start of TB treatment. The children were nil per mouth from midnight. A local anaesthetic jelly was applied before an indwelling catheter was inserted and blood drawn by the medical officer and assisted by the nursing sister on the study.

2.3.9.1 Pharmacokinetic study

RMP plasma concentrations were measured within a week of enrollment in the study and again four months after the start of TB treatment. The study's registered nurse administered the medication. Blood specimens were taken at intervals of 45 minutes, 90 minutes, 3, 4 and 6 hours after the dosing by the medical officer (MO). The blood specimens was immediately placed on ice and centrifuged within 30 minutes. A plasma sample of 1ml was stored in poly-propolene tubes at -80˚C and protected from light until analysed. The specimens were analysed for RMP by high pressure liquid chromatography with ultraviolet detection, measuring to 0.3 $\mu g.ml^{-1}$ of RMP, at the Department of Pharmacology at the University of Cape Town.

2.3.9.2 Biochemical analysis

The African Micronutrient Research Group laboratory of the Department of Human Nutrition at the University of Stellenbosch did the following analyses:

Vitamin A – Vitamin A was determined quantitatively by High Performance Liquid Chromatography. The coefficient of variation for standards used for the normal value was 3.7%.[77]

Vitamin C – Total ascorbic acid was determined spectrophotometrically by measuring the orange colour in a coupling with 2 – 4 – dinitrophenylhydrazine. The coefficient of variation for standards used for the normal value was 7.8%.[78]

Vitamin E – Vitamin E was determined quantitatively by High Performance Liquid Chromatography. The coefficient of variation for standards used for the normal value was 9.8%.[79]

Pyridoxine – Vit. B6 was determined enzymatically (Tyrozine decarboxylase) and measured by radioactive Tyrosine (C^{14}). The coefficient of variation for standards used for the normal value was 6.5%.[80]

PathCare Laboratories (Cape Town, South Africa) analysed the:

Magnesium – The Roche Hitachi 917 was used to determine magnesium by the Xylidyl-Blue reaction.[81] The coefficient of variation for standards used for the normal value was 2.3%.

Iron – Serum iron was determined by colorimetric assay.[82] The coefficient of variation for standards used for the normal value was 6.7%.

Haemoglobin – Flow-through technology or light scatter was used to determine haemoglobin with the Bayer Advia 120.[81] The coefficient of variation for standards used for the normal value was 2.3%.

Ferritin – Ferritin was determined by an antigen/antibody complex and turbidimetric measurement.[81] The coefficient of variation for standards used for the normal value was 5.0%.

Iron-binding capacity – IBC was calculated from serum iron and transferrin.[83] No coefficient of variation, as it is a calculated value.

AST – International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) method without pyridoxal phosphate.[84] The coefficient of variation for standards used for the normal value was 5.7%.

GGT – L-y-Glutamyl Transferase (5-amino-2-nitrobenzoate) SZASZ.[85] The coefficient of variation for standards used for the normal value was 7.0%.

ALT – IFCC method without pyridoxal phosphate.[86] The coefficient of variation for standards used for the normal value was 6.7%.

2.3.10 Assessment of HIV and immunological status

The HIV-status of some of the children was done before admission to BHCD. Counseling of the parents or legal guardians preceded HIV-testing and written informed consent was obtained. The counseling was done by the social worker of BHCD (in English or Xhosa) and the Medical Officer involved in the study (in Afrikaans or English).

If a child was tested HIV positive before enrolment in the study the information was obtained from the referring hospital's file and therefore we do not know what method was used to determine HIV-status. HIV status determined after enrolment in the study was done by enzyme-linked immunosorbent assay (ELIZA) by Pathcare (Cape Town, South Africa). HIV testing was done using the Abbott Axsym instrument, coefficient of variation is not applicable as only a positive or negative result is obtained.

The CD4 lymphocyte count was done by flow-cytometry and had a coefficient of variation of 25%. Immunological status was categorised by age as no evidence of suppression, moderate suppression or severe suppression.[87,88]

Table 2.1: Immunologic categories for HIV-infected children based on age-specific CD4 T-lymphocyte count

Immunologic catagory	Cells/µl		
	<12 months	1-5 years	6-12 years
No evidence of suppression	≥1 500	≥1 000	≥500
Evidence of moderate suppression	750 – 1 499	500 - 999	200 - 499
Severe suppression	<750	<500	<200

From: MMWR Vol. 46/ No. RR 12[87]

2.4 Data Analysis

Patient information was entered continuously during the course of the study by the researcher anonymously onto coded case report forms and computerized for analysis. Bio-equivalence, the occurrence of toxicity, nutritional and disease status and the outcome of disease management was compared between the two study groups (HIV-infected and HIV-non-infected). Data was recorded in an Excel spreadsheet and analyzed with STATISTICA version 8.0. Basic statistics like means, medians, quartiles and standard deviations was used to describe continuous and ordinal variables and frequency tables for nominal variables.

All bio-equivalence data points was analysed using paired t-test in the case of a normal distribution or Wilcoxon Sign Rank test in data not normally distributed. The bio-equivalence parameters were also subjected to Hauschler's analysis of the 95% confidence interval. When nominal variables were compared to other nominal variables appropriate chi-square tests was used. All statistical analyses were done with a significance level of 5%.

2.4.1 Analysis of anthropologic measurements

Information from the National Centre for Health Statistics (NCHS) was used to generate Z-scores and to determine the nutritional status of the children. Malnutrition was defined as stunting, wasting or underweight as defined by the NCHS classifications recommended by the WHO[66,68]. Height for age (H/A), weight for age (W/A) and height for weight (W/H) indicators

were expressed as z-scores or standard deviations (SD) below the median NCHS/WHO international reference standard.

Children were classified as severely malnourished if the z-scores were more than 3 standard deviations (SD) below the median NHCS/WHO international reference standard. Z-scores between -2.0 and -2.99 SD below the median NHCS/CDC/WHO international reference standard were classified as moderately malnourished

Stunting (H/A ≤-2SD) was used to indicate an overall slowing of skeletal growth that occured over a long period of time. Wasting (W/H ≤-2SD) was used to signify a loss in tissue and fat mass that occurred over a shorter period of time. Underweight (W/A≤-2 SD) was used as an indicator of poor weight gain within a particular age group.

Skinfold thickness measurements were used to determine body composition and to evaluate changes in the distribution of fat in the disease groups. The assumption is made that triceps skinfold (TSF) and subscapular skinfold (SSF) measures energy reserves stored as fat and arm muscle area (AMA) reflect reserves stored as muscle protein. Values were compared to percentiles from the United States Health and Nutrition Examination Survey I.[72] Values under the 25th percentile were seen as indicative of low protein or fat reserves.[89]

2.4.2 Dietary analysis

Once the researcher had ensured that all data were collected and questionnaires completed fully, data recorded on the FFQ and 24-hour recall questionnaire was entered into the computer using Foodfinder III software, designed by MRC. The data entered was crosschecked to ensure correct entry coding and correct quantities.

All dietary data was quantified using the South African RNID food composition tables. Energy was compared with the Recommended Dietary Allowance (RDA) values, the standard approach used at the time for the purpose. The dietary data are expressed as recommended daily intake per age group. Nutrient intake was compared using the RDA reference where a cut-off point of 67% of the recommended intake was used to describe inadequacy of nutrient intake.[94]

2.4.3 Anti-tuberculosis drugs

Published reference ranges for RMP have suggested that 2 hour concentrations of <8µg/ml should be regarded as low and <4µg/ml as very low.[90] As all the children's values was low, it was decided to classify low RMP values as <4µg/ml. INH levels of <3.0µg/ml at 2 hours was classified as low.[90]

2.5 Ethics Considerations

The Committee for Human Research of the University of Stellenbosch approved the study (2003/054/N).

2.5.1 Informed consent

The parents or legal guardians gave written informed consent for the children's participation in the study and for HIV testing if the child's HIV status was not known. A child was excluded from the study if written informed consent to participate was refused or could not be obtained. The consent forms were translated into Afrikaans and Xhosa for non-English speaking participants. Written informed consent were obtained after the information sheet had been explained in English or Afrikaans by the Medical Officer involved in the study. For Xhosa speaking parents or legal guardians who did not understand English or Afrikaans, the Xhosa informed consent form and information sheet were explained by a Xhosa-speaking nursing sister (Appendix 1).

2.5.2 Patient confidentiality

Patient confidentiality was protected by anonymous coding of specimens. Demographic and clinical data was stored in the researchers' office at BHCD making use of anonymous coding. The data was only accessible by the researchers.

CHAPTER 3: RESULTS

3.1 Sample Characteristics

Sixty children, 26 HIV-infected and 34 HIV-uninfected were enrolled in the study. Four children (all HIV-infected) were transferred back to referring hospitals shortly after enrolment due to complications that could not be handled at BHCD and three children were discharged from hospital after completion of the first pharmacokinetic study. As a result these seven children were excluded from the study and their data not included in the analysis. Results from anthropometric data for the remaining 19 HIV-infected and 34 HIV-uninfected children were included in the final analysis. Liver enzyme analyses were not done for 2 children at enrolment and 3 at 4 months, while vitamin status was not determined for 1 child at enrolment and 2 at 4 months and they were therefore not included in the analysis.

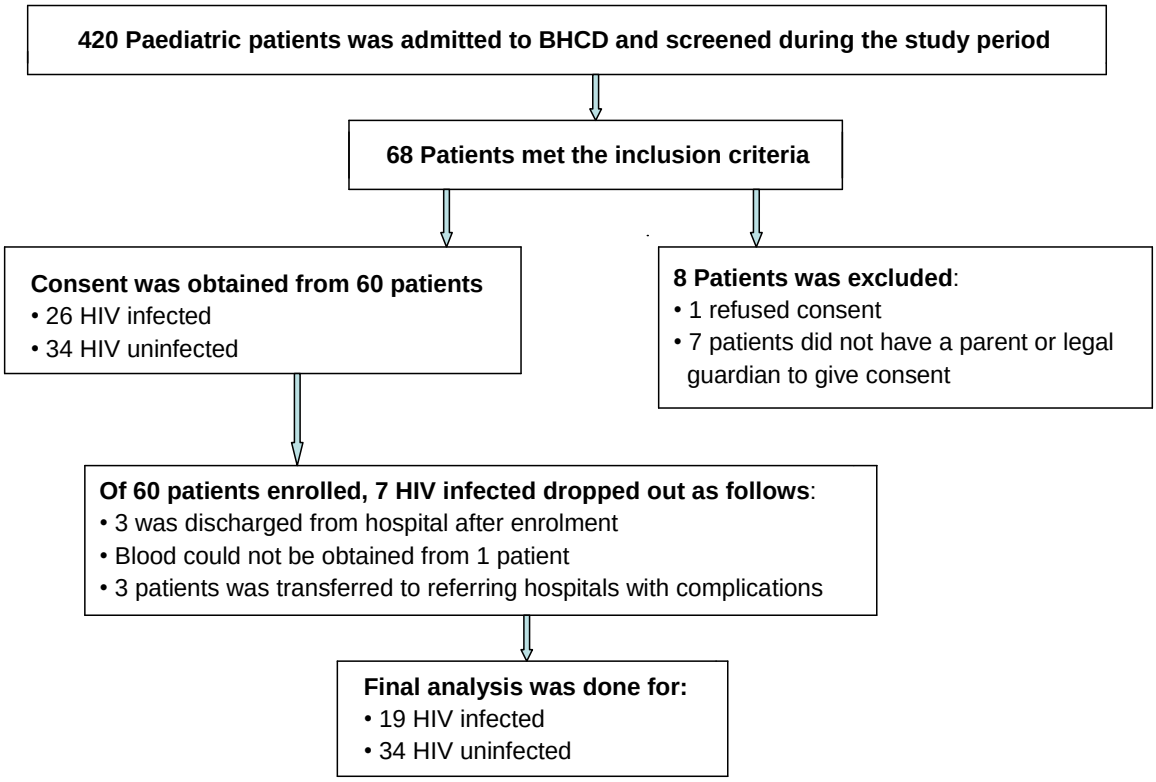

Figure 3.1 Characteristics of sample

3.2 Demographic, Diagnostic and Clinical Features

Demographic, diagnostic and clinical features of the children studied are summarized in Table 3.1. Of the 53 children studied, 29 were male and 24 were female. HIV positive children comprised 35.8%, whereas 64.2% were HIV negative. The ages of the children studied ranged from 5 months to 12 years, with more than 50% under 4 years of age. The age distribution indicates that the largest number (26.4%) of children were in the 48-72 month category, followed by those between 24-48 months of age (24.5%). The period between the start of treatment and enrolment in the study did not differ between the HIV positive and HIV negative children and was 34.2 days and 38.0 days respectively.

Overall a culture of *M tuberculosis* was obtained from 28 (53.8%) children and in a further 3 HIV-uninfected children with negative cultures, acid fast bacilli (AFB) were seen on microscopy of gastric aspirates. Household TB contact was high (69.8%) and did not differ significantly between the HIV-infected and HIV-uninfected children (p=0.82). Pulmonary TB was more common in the HIV-infected children (94.7%) compared to 79.4% of HIV-uninfected children but the difference was not significant (p=0.72), but tuberculous meningitis was more frequent in the HIV-uninfected children than HIV-infected children, with 55.8% and 36.8% respectively, but this difference was also not significant (p=0.16). Culture and microscopy were not carried out on 3 HIV-uninfected children. Mantoux test was not read in one HIV-uninfected child and, as expected, only a minority (22%) of HIV-infected children had a positive Mantoux test.

Table 3.1: Demographic, diagnostic and clinical features of children with and without HIV-infection

		HIV positive with TB *N*=19 (%)	HIV negative with TB *N*=34 (%)	Total *N* (%)	P-value
Gender	Male	11 (37.9)	18 (62.1)	29 (54.7)	
	Female	8 (33.3)	16 (66.6)	24 (45.3)	
Total		19 (35.8)	34 (64.2)	53	
Age (in months)	6-<12	2	4	6 (11.3)	
	12-<24	3	7	10 (18.9)	
	24-<48	6	7	13 (24.5)	
	48-<72	7	7	14 (26.4)	
	≥72	2	8	10 (18.9)	
Days from start of treatment to enrolment in study		34.2	38.0		0.49
Culture of *M tuberculosis* or AFB seen on microscopy		10 (41.6) 24 done	18 (64.2) 28 done	28 (53.8)	0.16
Household TBcontact		14 (73.6)	23 (67.6)	37 (69.8)	0.82
Clinical features	Intra-thoracic TB	18 (94.7)	27 (79.4)	45 (84.9)	0.72
	Tuberculous meningitis	7 (36.8)	19 (55.8)	26 (49.1)	0.16
Mantoux test	≥15mm	2 (10.5)	30 (88.2)	32 (60.3)	<0.001
	10-14mm	2 (10.5)	-	2 (3.7)	
	5-9mm	-	-	-	

Section A: Baseline

3.3 Baseline Features (Table 3.2)

3.3.1 Immunological status

The mean CD4 count of the 19 HIV-infected children at enrolment was 515.7μl^{-1}. According to the age-specific T-lymphocyte counts of the children, the largest proportion was classified as severely compromised immunity (47.4%), followed by 31.6% moderately compromised immunity and 21.0% had no immuno-suppression. (Appendix 4)

3.3.2 Anthropometry

MUAC was low in 20.8% of HIV-infected patients and 23.5% of HIV-uninfected patients, and the difference was not significant (p=0.410). There was no significant difference in stunting or wasting between HIV-infected and HIV-uninfected children, but underweight for age was significantly more common (p=0.003) amongst the HIV-infected children (31.5%) than amongst the HIV-uninfected children (2.9%). between and. (Figure 3.2)

The difference in low (under the 25th percentile) AMA between HIV-infected (84.2%) and HIV-uninfected (79.4%) children was not significant with a p-value of 0.665. TSF was low in 63.1% of HIV-infected patients and 41.2% HIV-uninfected patients (p=0.123 not significant). A significant difference (p=0.039) in the frequency of low SSF was seen between HIV-infected (26.3%) and HIV-uninfected (5.8%) children. Muscle mass, as measured by AMA was therefore more depleted in both groups than fat mass at enrolment.

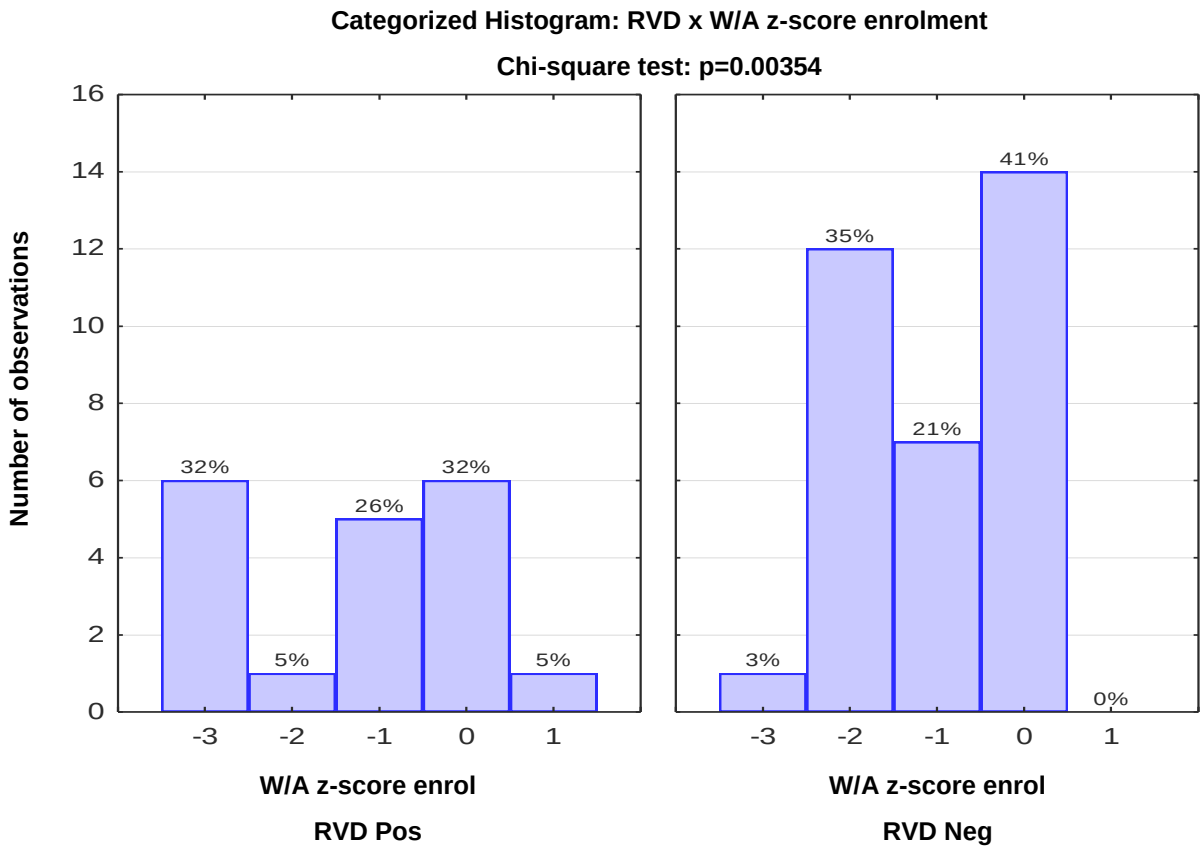

Figure 3.2 Effect of HIV-status on underweight (W/A)

3.3.3 Ultrasound

Abdominal nodes were indicating abdominal TB involvement were visualized on ultrasound in 36.8% of HIV-infected children with 26.4% of HIV-uninfected children (p= 0.43354). A total of 30.2% had abdominal involvement at enrolment. All of the HIV-uninfected children had one area of abdominal involvement, while 57% of HIV-infected children had two or three areas of involvement, including the liver, spleen and kidneys. (Table 3.2)

Abnormal abdominal ultrasound showing abdominal lymph-node enlargement was compared to nutritional status. Nutritional status, as determined by weight for height (p=0.41), weight for age (p=0.1099) and height for age (p=0.2271), was not significantly affected by abdominal lymph-node involvement.

3.3.4 Liver enzymes

AST was elevated in 29.4% of children studied. There was a marked, but insignificant (p=0.0541) difference between the raised level of AST in HIV-infected (47.1%) and HIV-uninfected (20.5%) children. Despite the increased values on enrolment only two HIV-infected and two HIV-uninfected children had ALT values increased >X3 normal. Similarly AST values >X3 normal were found in only one HIV-infected child and two HIV-uninfected children. HIV infection had no effect on the raised levels of ALT (11.7%) and GGT (35.2%) of the children. (Table 3.2)

3.3.5 Biochemical values

More than 30% of the children had sub-optimal vitamin A, pyridoxine and haematocrit levels. Magnesium, iron and haemoglobin levels were sub-optimal in over 50% of the children studied. It is notable that no children in either group had lower than normal zinc levels at enrolment and that selenium, vitamin C and vitamin E values were normal except for a small minority of children. (Table 3.2)

A marked, but not significant, difference was seen in pyridoxine (p=0.0738), IBC (p=0.1426) and Hb (p=0.5148) levels between HIV-infected and HIV-uninfected children. A larger number of HIV-infected than HIV-uninfected children had sub-optimal levels of pyridoxine, IBC and Hb. Low ferritin levels (p=0.0208) were significantly more prevalent in the HIV-uninfected children, at 30.3%, compared to 5.2% HIV-infected children. Low Hct levels were significantly more prevalent (p=0.00001) in HIV-infected (78.9%) children compared to HIV-uninfected (14.7%) children at enrolment. (Table 3.2)

Table 3.2: Anthropometric, ultrasound and biochemical characteristics of children at baseline

		HIV positive with TB *N* (%)	HIV negative with TB *N* (%)	Total *N* (%)	P-value
CD4 count (mean)		515.7 μl^{-1}			
Anthropometry	MUAC (≤13.5cm)	5 (20.8)	8 (23.5)	13 (24.5)	0.410
	Stunted	6 (31.5)	5 (14.7)	11 (20.7)	0.449
	Wasted	1 (5.2)	0	1 (1.8)	0.766
	Underweight	6 (31.5)	1 (2.9)	7 (13.2)	0.003
	AMA <25th percentile	16/19 (84.2)	27/34 (79.4)	43/53 (81.1)	0.6651
	TSF <25th percentile	12/19 (63.1)	14/34 (41.2)	26/53 (49.1)	0.1231
	SSF <25th percentile	5/19 (26.3)	2/34 (5.8)	7/53 (13.2)	0.0390
Abdominal nodes visualized on ultrasound		7 (36.8)	9 (26.4)	16 (30.2)	0.4335
Liver enzymes (elevated)	AST	8/17 (47.1)	7/34 (20.5)	15 (29.4)	0.0541
	ALT	2/17 (11.7)	4/34 (11.7)	6 (11.7)	0.8274
	GGT	6/17 (35.2)	12/34 (35.2)	18 (35.2)	0.3826
Biochemical (sub-optimal levels)	Vitamin A	7/19 (36.8)	10/33 (30.3)	17 (32.6)	0.0590
	Vitamin C	0/19 (0)	1/34 (2.9)	1 (1.8)	0.2520
	Vitamin E	2/19 (10.5)	4/33 (12.1)	6 (11.5)	0.6022
	Pyridoxine	10/19 (52.6)	6/34 (17.6)	16 (30.1)	0.0738
	Selenium	0/19 (0)	2/30 (6.6)	2 (4.08)	0.4125
	Magnesium	13/16 (81.2)	26/33 (78.7)	39 (79.5)	0.8402
	Zinc	0/19 (0)	0/33 (0)	0	0.4738
	Fe	11/19 (57.9)	22/33 (64.7)	33	0.6602
	IBC	4/16 (25)	2/33 (6.1)	6 (12.2)	0.1426
	Hct	15/19 (78.9)	5/34 (14.7)	20 (37.7)	0.00001
	Ferritin	1/19 (5.2)	10/33 (30.3)	11 (21.1)	0.0208
	Hb	16/19 (84.2)	18/34 (52.9)	34 (64.1)	0.5148

3.3.6 Dietary intake

The researcher often did not have direct contact with the parent or guardian of a child as the enrolment and initial interview was done by the Medical Officer of the larger study in which this study was nested. The 24-hour recall and food frequency questionnaire (FFQ) at the time of enrolment was therfore not done for all children. Diet histories, including a food frequency questionnaire and 24-hour recall could only be obtained from 15 children, 9 HIV-uninfected and 6 HIV-infected. The data from these questionnaires was compared (Table 3.3) to the average daily intake from the 3 week cycle menu of BHCD at the time of the study.

Intake of less than 67% of the recommended dietary allowance (RDA) was defined as low. The BHCD diet contributed more than 67% of macro- and micronutrients, i.e the minimum, in all cases, but only met 100% of RDA for protein, magnesium, vitamin A and vitamin C.

From the FFQ the children's usual dietary intake of zinc and vitamin E was low. The FFQ indicated 100% of the RDA for protein was met by 80% of children and 86.67% reported 100% RDA intake of magnesium. The 24-hour recall showed similar results, 86.67% met 100% RDA for protein and 80% met 100% RDA for magnesium. The 24-hour recall showed that less than 60% of respondents consumed 100%of RDA for energy, iron, zinc, selenium, pyridoxine and vitamins A,C and E. According to the 24-hour recall all of the selected nutrients listed in Table 3.3 were ingested in amounts higher than 67% of the RDA. The amount of protein reported was especially high at 255.1% and 317.1% of the RDA from the FFQ and 24-hour recall, respectively.

Table 3.3 Comparison of mean dietary intake derived from Food frequency questionnaire, 24-hour recall and BHCD diet, expressed as percentage of age-specific RDA at baseline

Nutrient	Food frequency questionnaire			24-hour recall			BHCD
	Mean (SD)	Median	100% RDA met, *N=15* (%)	Mean (SD)	Median	100% RDA, met, *N=15* (%)	
Energy	86.1 (103.5)	57.0	4 (26.67)	103.7 (100.5)	70.7	2 (13.33)	68.3
Protein	255.1 (427.9)	129.2	12 (80.00)	317.1 (382.1)	201.7	13 (86.67)	212.9
Iron	92.3 (160.0)	41.0	4 (26.67)	152.9 (240.6)	60.0	2 (13.33)	71.0
Magnesium	215.0 (301.5)	127.5	13 (86.67)	247.9 (270.1)	160.0	12 (80.00)	157.5
Zinc	62.9 (87.1)	39.5	2 (13.33)	92.7 (97.6)	64.5	1 (6.67)	96.7
Selenium	132.7 (212.8)	59.5	5 (33.33)	96.1 (97.8)	60.3	5 (33.33)	82.0
Vitamin A	186.1 (277.0)	103.8	9 (60.00)	253.2 (291.9)	152.1	8 (53.33)	120.6
Vitamin C	108.8 (117.0)	77.5	6 (40.00)	194.1 (296.6)	73.3	5 (33.33)	106.6
Vitamin E	54.0 (48.4)	39.7	3 (20.00)	116.0 (164.8)	66.0	2 (13.33)	85.3
Pyridoxine	71.6 (88.7)	47.5	3 (20.00)	87.7 (90.8)	54.6	1 (6.67)	94.9

3.3.6.1 Diet history

The nutritional status of the children from whom a diet history could be obtained, as classified by anthropometric z-scores, was not consistent with the nutritional status of the study sample.

(Table 3.4) The information obtained from the diet history can therefore not be extrapolated to the whole sample studied.

Table 3.4 Comparison of nutritional status in diet history sample to total study sample

Classification	Enrolment	
	Diet history obtained, *N=15* (%)	Children studied, *N*=53 (%)
Normal	13 (86.6)	35 (66.0)
Stunted	1 (6.6)	11 (20.7)
Underweight	1 (6.6)	7 (13.2)
Wasted	0 (0.0)	0 (0.0)

Two children from which a diet history was obtained was classified as malnourished. Energy intake from the FFQ was low (57.0% of RDA) in the underweight child, while protein intake was normal (106.2% of RDA). The stunted child had a energy intake of 72.1% of RDA and protein intake of 151.3% of RDA.

Section B: Follow up

3.4 HIV Status of Children

The immunological status of HIV-infected children was tested at enrolment and after four months of treatment. The CD4 counts of HIV-negative children were not determined. The clinical presentations of the HIV-infected children varied during the period of hospitalization. The mean CD4 count of the 19 HIV positive children was 515.7μl^{-1} at enrolment and the mean of the 18 at month 4, 589.5μl^{-1}.

Table 3.5 indicates that 31.6% of HIV-positive children were classified as moderately immuno-compromised at enrolment, compared to 55.5% at 4 months of treatment. At enrolment the immunity of 47.4% was severely compromised, which decreased to 27.8% at month 4. The CD4 count of 1 child was unknown at 4 months follow-up. Age-specific immunologic categories are given in Appendix 4.

HAART was commenced within the first 4 months of evaluation in 7 HIV-infected children, while 2 had been on treatment for at least two years before admission. A further 6 children commenced on HAART after the 4 months evaluation and 4 children were not placed on HAART. The mean CD4 count of the children started on HAART increased from 538.9μl^{-1} to 675.1μl^{-1}, which was not significant. One child's CD4 count decreased. Of these 7 children, 57.1% were severely immunocompromised and 28.6% were moderately immunocompromised at enrolment compared to 28.6% and 42.9%, repectively, at month 4.

Table 3.5: The age-specific immunological status of HIV-positive children studied

Immunologic category	Enrolment, *N* (%)	Month 4, *N* (%)
No immuno-suppression	4 (21.0)	3 (16.7)
Moderately compromised immunity	6 (31.6)	10 (55.5)
Severely compromised immunity	9 (47.4)	5 (27.8)
Total	19	18

3.5 Nutritional Status

3.5.1 Anthropometry

Anthropometric measurements were taken at enrolment and once a month thereafter. Only results at enrolment and 4 months after the start of TB treatment are included, as it is compared with data of the pharmacokinetic study which was only taken at these intervals.

3.5.1.1 Weight, height and MUAC

According to, HIV-status did not have a significant effect on the mean mid-upper arm circumference measurements at enrolment (P=0.41) or month 4 (P= 0.76). (Table 3.6)

Z-scores were used to classify malnutrition in this study. Stunting (46.27%) and underweight (34.51%) were identified as the most common types of malnutrition in both HIV-positive and HIV-negative children studied (Table 3.7). Severe malnutrition, classified as z-score <-3 SD below the mean NHCS/CDC/WHO International reference standard, was uncommon. None of the children were severely wasted or severely underweight. Severe stunting did occur in 1 (5.2%) HIV-positive child and 2 (5.8%) HIV-negative children, improving at month 4 when no HIV-positive children were severely stunted and only 1 (2.9%) HIV-negative child.

The effect of HIV-infection on malnutrition was not significant, except for underweight for age at enrolment with a p-value of 0.00354. At month 4 the effect of HIV-infection on underweight was not significant (p=0.5474).

There was no change in the number of stunted, wasted or underweight children from enrolment to month 4, indicating that there was very little or no catch-up growth on treatment in HIV-positive or HIV-negative children (Figures 3.3-3.5).

The mean weight of HIV-infected children at enrolment was 12.6kg, which increased to 13.1kg at month 4. HIV-uninfected children showed a significant increase from 13.9kg at enrolment to 15.0kg at month 4 (p=0.0013).

Table 3.6: The mean mid upper arm circumference at enrolment and at month 4 of study

	Enrolment			Month 4		
	HIV-positive	HIV-negative	P-value	HIV-Positive	HIV-negative	P-value
N	19	34		19	34	
MUAC in cm (SD)	11.67 (1.72)	12.10 (1.96)	0.41	12.57 (2.17)	12.77 (2.58)	0.76

Table 3.7: Percentage of children malnourished using z-scores, at enrolment and at month 4

Classifi-cation	**Enrolment *N* (%)**				**Month 4 (%)**			
	HIV-pos, *N=19*	HIV-neg, *N=34*	Total,*N= 53*	P-value	HIV-pos, *N=19*	HIV-neg, *N=34*	Total,*N= 53*	P-value
Stunted (H/A)	6 (31.57)	5 (14.70)	11 (20.75)	0.4496	6 (31.57)	5 (14.70)	11 (20.75)	0.4189
Wasted (W/H)	1 (5.26)	0 (0.0)	1 (1.88)	0.7666	1 (5.26)	0 (0.0)	1 (1.88)	0.1973
Under-weight (W/A)	6 (31.57)	1 (2.94)	7 (13.2)	0.0035	4 (21.05)	3 (8.82)	7 (13.2)	0.5474
Stunted and wasted	0 (0.0)	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	0 (0.0)	

Malnutrition classified as z-scores <-2 SD below the mean NHCS/CDC/WHO International reference standard.

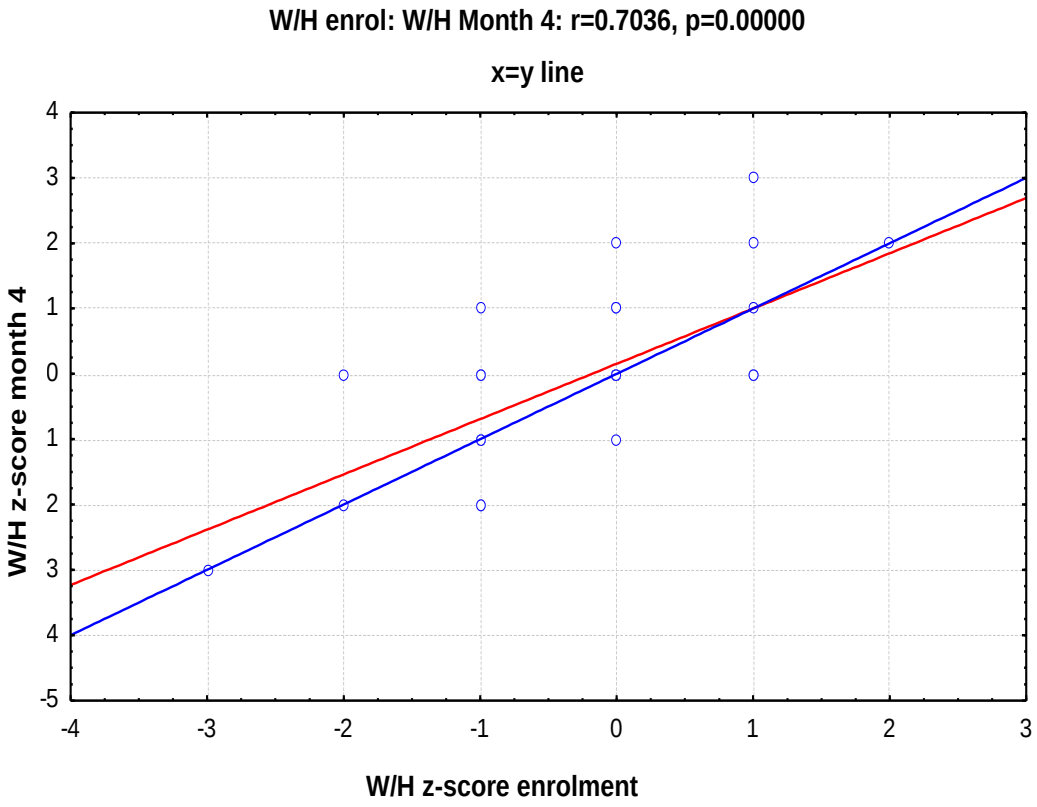

Figure 3.3 Relationship between wasting at enrolment and month 4

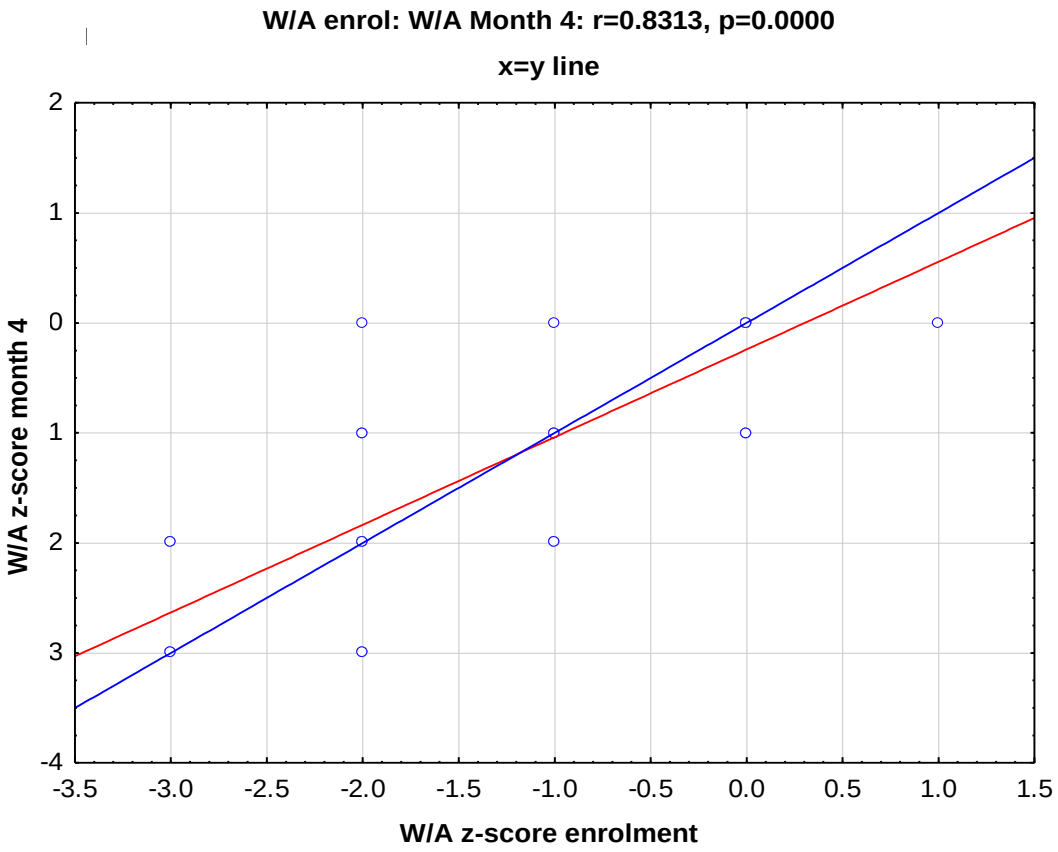

Figure 3.4 Relationship between underweight at enrolment and month 4

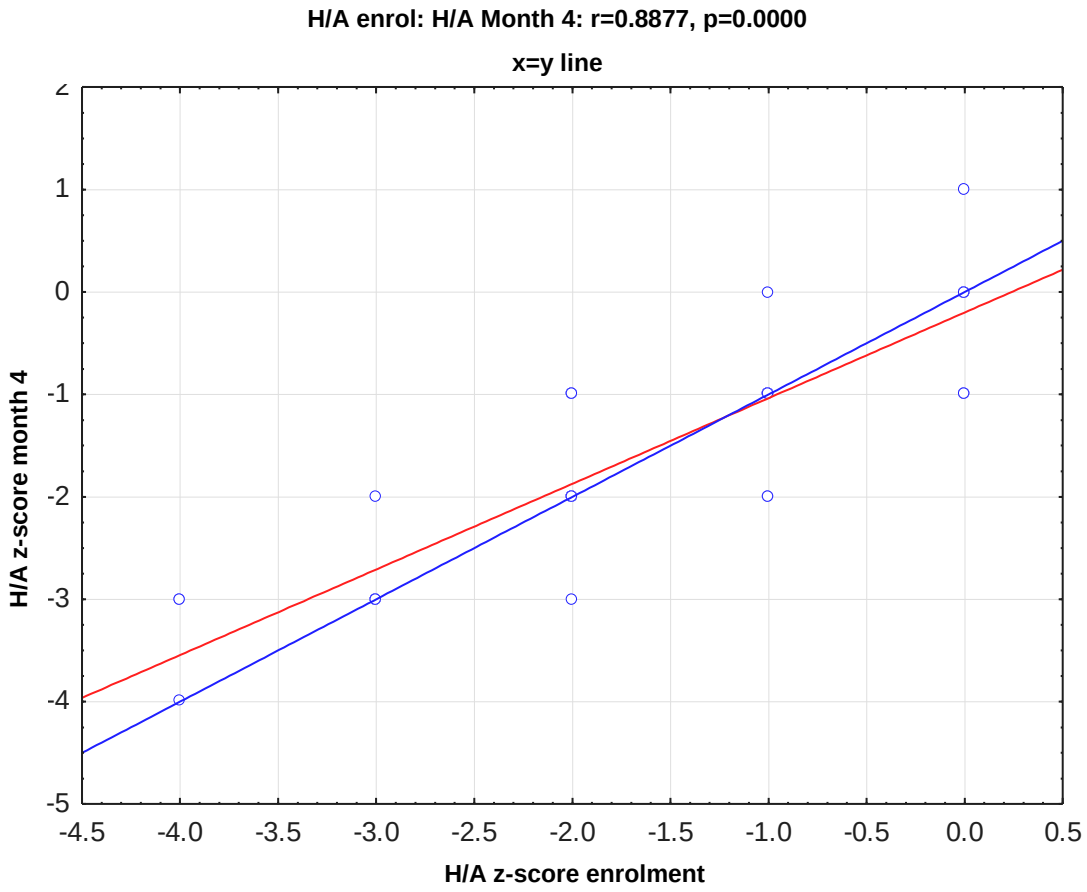

Figure 3.5 Relationship between stunting at enrolment and month 4

3.5.1.2 Body composition

At enrolment muscle mass, as measured by AMA, was more depleted in both groups than fat mass (Table 3.8). AMA increased in both groups after 4 months, but more so in the HIV-uninfected group. By 4 months the TSF decreased in the HIV-infected group, showing a decrease in fat stores, but this measurement increased in the HIV-uninfected group, showing an increase in fat stores, although not significantly (Table 3.8). Low values are classified as below the 25th percentile.

Table 3.8: Skinfold measurements and AMA

Measurement	Enrolment			Month 4		
	HIV-positive *N* (%)	HIV-negative *N* (%)	P-value	HIV-positive *N* (%)	HIV-negative *N* (%)	P-value
AMA (<25th percentile)	17/19 (89.4)	27/34 (79.4)	0.6651	15/20 (75.0)	22/34 (64.7)	0.4982
TSF (<25th percentile)	12/21 (57.1)	14/34 (41.2)	0.1231	12/20 (60.0)	13/34 (38.2)	0.5184
SSF (<25th percentile)	8/20 (40.0)	4/34 (11.7)	0.0390	7/20 (35.0)	5/34 (14.7)	0.0951

3.6 Liver functions

The anthropometric status of the children was compared to the liver enzymes at enrolment and 4 months (Table 3.9) of treatment. Weight for age had a significant negative effect on AST and ALT at enrolment with p-values of 0.02166 and 0.02765 respectively. Wasting had a significant negative effect on GGT at enrolment (p=0.03014). Stunting did not have a significant effect on liver enzymes. Anthopometric status did not have a significant effect on liver enzymes at month 4. (Table 3.9)

Table 3.9: Elevated liver enzymes compared with nutritional status at enrolment and month 4

Liver enzyme (normal values)	**Enrolment**				**Month 4**			
	Stunted *N* (%)	Wasted *N* (%)	Under-weight *N* (%)	Normal *N* (%)	Stunted *N* (%)	Wasted *N* (%)	Under-weight *N* (%)	Normal *N* (%)
AST (16-46 μl^{-1}) p-value	5 (45.5) 0.5906	1 (100.0) 0.1858	5 (71.4) 0.0216	5	2 (22.2) 0.8188	0 (0.0) 1.0000	1 (14.3) 0.2498	6
ALT (3-37 μl^{-1}) p-value	3 (27.3) 0.0714	0 (0.0) 0.9417	2 (28.6) 0.0276	1	3 (33.3) 0.6210	0 (0.0) 0.5114	2 (28.6) 0.0722	4
GGT (1-32 μl^{-1}) p-value	5 (45.5) 0.5664	1 (100.0) 0.0301	5 (71.4) 0.1044	4	4 (44.4) 0.4587	1 (100.0) 0.1172	4 (57.1) 0.1554	6
Total	13	2	12	10	9	1	7	16

HIV-infection had a significant effect on AST at month 4 (Figure 3.6), with 41% of HIV-infected children having elevated AST-levels (p-value 0.02477).

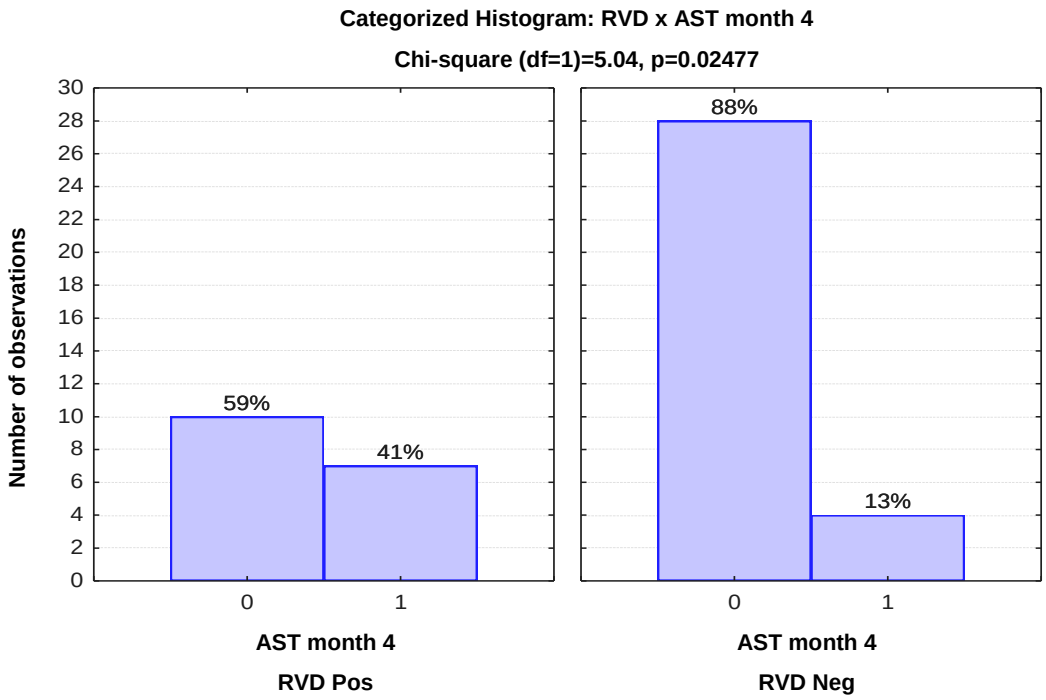

Figure 3.6 Effect of HIV-infection on AST at month 4. 0 indicates normal values (16-46 μl^{-1}) and 1 are elevated values.

3.7 INH-levels

INH-levels at enrolment and after 4 months (Table 3.10) of treatment were compared to nutritional status to determine whether nutritional status had an effect on the bio-availability of anti-tuberculosis agents. Values of <3.0µg/ml at 2 hours after ingestion was considered low.

None of the parameters used to determine nutritional status had a statistically significant effect on INH-levels. In stunting, wasting and underweight INH-levels were normal in more than 50% of children. At 4 months none of the malnourished children had low INH levels.

Table 3.10: INH levels compared to nutritional status (%)

INH-level	Enrolment			Month 4		
	Wasted *N* (%)	Stunted *N* (%)	Under-weight *N* (%)	Wasted *N* (%)	Stunted *N* (%)	Under-weight *N* (%)
INH low	0 (0)	2 (18.18)	1 (14.28)	0 (0)	0 (0)	0 (0)
INH normal	1 (100)	6 (54.54)	4 (57.14)	1 (100)	9 (81.81)	5 (71.42)
INH high	0 (0)	3 (27.27)	2 (28.57)	0 (0)	2 (18.18)	2 (28.57)
Total	1	11	7	1	11	7

*Kruskal-Wallis test, p> 0.05

3.8 Rifampicin (RMP) levels

RMP levels and abnormal nutritional status parameters were compared to determine a possible link between malnutrition and low blood levels of RMP. RMP concentrations of <4µg/ml was regarded as low. A statistically significant effect of malnutrition on RMP-levels could not be determined. (Table 3.11)

Table 3.11: RMP levels compared to nutritional status (%)

RMP-level	Enrolment			Month 4		
	Wasted *N* (%)	Stunted *N* (%)	Under-weight *N* (%)	Wasted *N* (%)	Stunted *N* (%)	Under-weight *N* (%)
RMP low (<4µg/ml)	1 (100)	3 (42.85)	1 (50)	1 (100)	4 (57.14)	1 (50)
RMP (≥4µg/ml)	0 (0)	4 (57.14)	1 (50)	0 (0)	3 (42.85)	1 (50)
Total	1	7	2	1	7	2

* Kruskal-Wallis test, p> 0.05

3.9 Biochemical

Biochemical values of the children were compared between HIV-infection groups at enrolment and at 4 months after hospitalization. The mean values of selected biochemical analyses are indicated in Table 3.12. HIV-infection had a marginally significant effect on selenium, IBC and ferritin means at enrolment, with p-values of 0.030, 0.025 and 0.026, respectively. At the assessment 4 months after the start of anti-TB treatment, HIV-infection had a significant effect on the mean vitamin C, selenium, pirydoxine and ferritin levels, with p-values of 0.005, 0.012, 0.001 and 0.002, respectively.

Table 3.12: Mean Biochemical values at Enrolment and Month 4 of observation

	Enrolment			**Month 4**		
	HIV positive	HIV negative	P-value*	HIV positive	HIV negative	P-value*
Vitamin A (>20µg.dl^{-1})	24.68	26.54	0.5225	22.61	27.02	0.0591
Vitamin C (0.25-1.20mg.dl^{-1})	0.89	1.04	0.2520	0.75	1.02	0.0050
Vitamin E (>6mg.l^{-1})	9.63	9.23	0.6022	8.20	9.35	0.1252
Pyridoxine (6-20ng.ml^{-1})	8.32	11.28	0.1189	6.75	14.76	0.0010
Selenium (46-143µg.l^{-1})	69.00	91.9	0.0308	75.11	108.51	0.0126
Magnesium (0.6-1.0mmol.l^{-1})	0.92	0.93	0.8100	0.82	3.57	0.3105
Zinc (7-22µmol.l^{-1})	18.57	18.03	0.7513	16.15	17.99	0.1354
Fe (9.5-21.3µmol.l^{-1})	11.12	8.79	0.2998	12.50	12.01	0.8423
IBC	49.94	57.17	0.0254	48.98	53.23	0.1207
Hct (0.33-0.39)	0.31	0.36	0.7525	0.31	0.36	0.7525
Ferritin (20-300µg.l^{-1})	72.04	36.54	0.0267	77.95	31.45	0.0028

* Welch two sample t-test

3.10 Diet history

No follow-up data was collected. As all the children were hospitalised at BHCD, the hospital diet was analysed and used for comparison.

CHAPTER 4: DISCUSSION AND LIMITATIONS

This study aimed to assess the nutritional status of children with TB, with and without HIV-infection, and to determine the effect that poor nutritional status has on absorption of anti-tuberculosis agents, hepatotoxicity and the effect of abdominal lymph-node involvement on nutritional status. Malnutrition was evident in 24.52% of the children. HIV-infection had a significant negative effect on weight for age, but other anthropometric indicators were not affected. Anthropometric parameters were found not to have an effect on blood levels (absorption) of anti-tuberculosis agents. Elevated liver enzymes indicating hepatotoxicity were affected by wasting and underweight, but stunting did not have a significant effect. Nutritional status was not affected by abdominal lymph-node involvement as determined by ultrasound.

The most prevalent forms of malnutrition in this study were stunting and underweight. No change occurred in the amount of stunting and wasting from enrolment to month 4 of the study and only a small and insignificant change was found in underweight for age. HIV-infection did not have a significant effect on stunting or wasting, but did significantly affect weight for age at enrolment. Mean weight gain was significant in HIV-uninfected children. This shows that there was no or very little catch-up growth in the HIV-infected group during the time on treatment. The fact that the HIV- infected group showed no catch-up growth highlights the many factors possibly contributing to failure to thrive. One of the contributing factors may be a sub-optimal hospital diet and needs to be further investigated.

The assumption was made that triceps skinfold and subscapular skinfold measurements indicate energy reserves stored as fat, and arm muscle area reflect muscle protein stores. Muscle mass was more depleted at enrolment than fat mass in HIV-positive and HIV-negative children. Muscle mass increased by month 4, but more so in the HIV-negative group, indicating that HIV-uninfected children had a better response to adequate intake while on TB treatment. The severity of illness determines the metabolic stress in an individual. This may suggest that HIV-infected children is prone to more serious TB-infection or that HIV-infection exercises additional metabolic stress.

Fat distribution was disproportionate in both HIV-positive and HIV-negative children at enrolment, with subscapular skinfold higher in both groups than TSF. By month 4 the TSF decreased in the HIV-positive group, showing a decrease in fat stores, but these measurements

increased in the HIV-negative group, showing an increase in fat stores, although not significantly so. Preferential fat storage during recovery from catabolic stress has been reported[74] and should be further investigated in this age group to make a more definite conclusion. Many patients remain underweight after 6 months of TB treatment, even when treatment is successful.[74] An increase in fat stores would be expected on an adequate diet and treatment and the failure of the HIV-positive children to achieve this may be due to altered metabolism as part of the inflammatory and immune responses.

In HIV-infected children at enrolment severely compromised immunity was most prevalent, but this improved to moderately immuno-compromised being most prevalent at month 4. Therefore despite nutritional status not improving the immune-status of HIV-positive children improved in hospital. This may be due to better nutrition, less infections, adequate TB treatment or a combination thereof. HIV-infection did not have a significant effect on nutritional status in this study. Only a minority of children (31.57%) were placed on HAART towards the end of the evaluation and did not have a significant effect on the immunological status of the children.

A significant number of children with primary tuberculosis will also have involvement of the abdominal lymph nodes in addition to those in the chest as result of the retrograde spread of mycobacteria.[87,88] In most cases this does not lead to overt abdominal tuberculosis, but may compromise the lymphatic drainage of the gut and so contribute to the development of malnutrition or affect the absorption of drugs. Neither nutritional status nor serum concentrations of RMP or INH were significantly affected by abdominal lymph-node involvement determined by abdominal ultrasound.

Poor nutritional status is one of the most widely accepted risk factors for anti-tuberculosis therapy induced hepatotoxicity. Underweight for age had a significant effect on AST and ALT and wasting had a significant effect on GGT. After 4 months of treatment malnutrition had no effect on liver enzymes. Stunting, indicative of longstanding undernutrition had no effect on liver enzymes. As malnutrition did not have an effect on hepatotoxicity after 4 months of treatment, the initial effect might be due to the TB-infection in combination with malnutrition rather than malnutrition alone.

Selected vitamins' status was analyzed. There was a significant change in vitamin A and vitamin C from enrolment to month 4 of the study. Vitamin A status improved, but vitamin C decreased. It has been found that there may be a notable decline in vitamin C with stress, inflammation or disease.[91] Vitamin E and pyridoxine values did not change significantly, even though the children received a multivitamin syrup daily. The mean plasma pyridoxine concentration did not differ significantly between HIV-infected and HIV-uninfected children at enrolment. At the second assessment after 4 months treatment the mean pyridoxine concentrations differed significantly between HIV-infected and HIV-uninfected children. Plasma pyridoxine concentrations in HIV-infected children did not differ between those children who were, and were not, receiving HAART. The low plasma pyridoxine concentrations found may be the result of an ongoing acute phase response and not a vitamin B6 deficiency, but it has been found in adult HIV-infected patients that pyridoxine-intakes more than twice the recommended daily allowance are associated with improved survival.[91] Despite pyridoxine supplementation and a diet containing adequate amounts of pyridoxine , sub-optimal concentrations were still found after 4 months of treatment in 47% HIV-infected children compared 52% after one month of treatment. Sub-optimal concentrations improved from 18% after 1 month to 6% after 4 months' treatment in HIV-uninfected children. Additional pyridoxine supplementation of HIV-infected children receiving INH would be advisable.

In summary the nutritional categorization of children with TB, with or without HIV co-infection, did not improve during hospitalization, despite treatment of TB, although mean weight increased, significantly so in HIV-uninfected children. Further study is necessary to determine whether nutritional support can be improved to enable the children to have a better disease outcome.

CHAPTER 5: RECOMMENDATIONS

For future study the following should be considered:

- Increased sample size is recommended as more than 25% of HIV-positive subjects enrolled were not included in the final analysis.

- Vitamin status should be investigated further to evaluate the supplements given and the vitamin content of the hospital diet, focussing particularly on pyridoxine supplementation to HIV positive children.

- The nutritional status of all children with TB should be assessed and those with stunting or wasting should be referred for nutritional support.

- The diet at BHCD should be evaluated extensively and a dietitian should be involved in menu-planning to ensure provision of nutritionally adequate diets.

- BHCD needs a dietitian to detect, monitor and treat malnutrition in this facility and give training and support to care-givers when the children are discharged.

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APPENDICES

Appendix 1: Informed consent forms

BMS: Secure the Future

Paediatric HIV/TB Research Consortium

University of Cape Town /University of Stellenbosch

THE PHARMACOKINETICS AND TOXICITY OF ANTITUBERCULOSIS AGENTS AND OTHER CO-ADMINISTERED DRUGS IN CHILDREN, WITH AND WITHOUT HIV INFECTION AND THEIR RELATIONSHIP TO NUTRITIONAL STATE AND TO THE NAT2 ACETYLATOR GENOTYPE AND PHENOTYPE.

Short title: The pharmacokinetics and toxicity of antituberculosis agents in children, with and without HIV infection.

Informed Consent Documents.

Introduction

HIV/AIDS and tuberculosis are major health problems in South Africa. When they occur together they can make one another's outcome worse. There is uncertainty as to what are the best dosages of antituberculosis medicines that should be used in children with tuberculosis, both with and without HIV infection. On the one hand giving too little of the medicine may be insufficient to kill all of the tuberculosis germs and so lead to the recurrence of the tuberculosis; on the other hand giving too much of a medicine may cause toxic effects. It is also possible that children with HIV infection may be more prone to toxic side effects of the antituberculosis medicines. During this study we will measure the way that children with tuberculosis absorb and metabolise antituberculosis medicines and evaluate whether HIV infection and its complications, malnutrition or tuberculosis itself have any effect upon the way that children with tuberculosis absorb and react to antituberculosis medicines.

This study is sponsored by Bristol Myers Squibb – Secure the Future Foundation.

The doctors in charge of this study at this site are: Professor Peter Donald of theDepartment of Paediatrics and Child Health of the Faculty of Health Sciences, the University of Stellenbosch and Professor Gregory Hussey of the School of Child and Adolescent Health, University of Cape Town.

Before you decide if you want your child to be a part of this study, we want you to know about the study. You may choose not to be part of this study. No health care will be withheld for your child should you choose not to be part of the study. Your child will still receive the standard TB treatment used at this clinic / hospital.

This is a consent form. It gives you information about this study. The study staff will talk with you about this information. You are free to ask questions about this study at any time. If you agree to allow your child to take part in this study, you will be asked to sign this consent form. You will get a copy to keep.

Why is this study being done?

The purpose of this study is to evaluate the absorption of antituberculosis medicines in children with tuberculosis, both with and without HIV infection. We will also examine whether factors such as malnutrition, liver disease or the presence of tuberculosis lymph nodes in the abdomen affect the absorption of antituberculosis medicines, their toxicity or their ability to cure tuberculosis.

What will happen to my child and what will I have to do if my child is in this study?

If you decide to allow your child to take part in this study a number of investigations will be done. These will help us determine whether your child has HIV infection, how serious the infection is, whether he/she is malnourished, and whether there are signs of liver damage. We will also evaluate the function of the immune system by counting certain of the white cells in the blood. The absorption of the antituberculosis medicines will be studied by placing a needle in a vein and taking a small amount of blood 4 times during each of the two investigations. The amount of the medicine in the blood will then be measured. The test will be repeated about 2 months after the treatment of tuberculosis was started to see whether improvement in nutrition and the tuberculosis has made any difference to the absorption of the medicines. All of the above investigations will mean taking approximately 3 teaspoonfuls of blood from your child.

An X-ray of the chest and special X-ray of the abdomen will also be taken to evaluate the spread of tuberculosis in the body. Your child's stool will also be examined for worms and signs of poor ability to absorb food or the antituberculosis medicines. The urine will be examined regularly for signs of disease.

If the diagnosis of tuberculosis has not been established the stomach juice will be withdrawn through a tube on two successive mornings and the throat will be aspirated to try and grow, or see, the tuberculosis germ.

Your child will be examined for signs of poor nutrition once every month and your child will be examined every week for signs of toxicity caused by the antituberculosis medicines and a blood test to evaluate liver damage due to antituberculosis treatment will be done once a week for the first month of treatment and thereafter once a month until your child is discharged from hospital. This test requires about half a teaspoonful of blood.

Two months and six months after admission to Brooklyn Hospital some of the blood tests will be repeated. These include those for the evaluation of nutrition, immunity and liver damage. These tests will require about 2 teaspoonfuls of blood. The X-ray studies of the chest will be repeated 2 months, 4 months and 6 months after starting tuberculosis treatment. The X-ray of the abdomen will be repeated 4 months after starting treatment.

After 6 months treatment stomach juice and the throat will again be aspirated to confirm that your child's tuberculosis really has been cured.

Follow up visits

After discharge from Brooklyn Hospital you will be given an appointment to bring your child back to either Tygerberg Children's Hospital or the Red Cross Children's Hospital eighteen months

after the start of antituberculosis treatment. During this visit the chest X-ray and the blood tests to evaluate nutrition, immunity and liver damage will be repeated. These tests will also require about 2 teaspoonfuls of blood. A stool specimen will again be examined for worms and for signs of failure to absorb foods.

How many children will take part in the study?

About 100 children will be enrolled in the study.

How long will your child be in the study?

Your child will be in the study for eighteen months after starting antituberculosis treatment. If possible we would also like to follow your child up for a further three years to evaluate any long-term problems that might be caused by tuberculosis and antituberculosis treatment, but we understand that this might be difficult for you.

Why would the doctor take my child / baby off this study early?

The study doctor may need to take your child/baby off the study early without your permission if:

The study is cancelled by the site's Ethics Committee (the committee that watches over the safety and rights of research subjects).

A Data Safety Monitoring Board (DSMB) recommends that the study be stopped early (A DSMB is an outside group of experts who monitor the study).

Your child/baby is not able to attend the study visits as required by the study.

The study doctor decides that it is harmful for you child/baby to continue in the research study.

What are the risks of the study?

Adverse reactions to TB medication are relatively rare, but in some patients they may be severe. If your child/baby experience any of the side effects described below you must let the study doctor or nurse know immediately.

The side effects from the TB medication that you must report to the doctor or study nurse are: skin rash, blurred or changed vision, flu-like symptoms and fever for more that 3 days, stomach ache and upset, nausea and vomiting, lack of appetite, joint aches, bruises, dizziness, tingling and numbness around the mouth, tingling sensation in the hands and feet. One of the TB drugs, Rifampicin, that your child/baby will receive, will colour the urine, sweat and tears orange.

Are there benefits to taking part in this study?

If your child/baby takes part in this study, there may be a direct benefit to your child/baby, but no guarantee can be made. It is also possible that your child/baby may receive no benefit from being in this study. Information learned from this study may help other children and babies who have HIV and TB infection or TB without HIV-infection.

What other choices does my child/baby have besides this study?

Instead of being in this study you have the choice of TB treatment available to your child/baby at this hospital / clinic. Please talk to your doctor about these and other choices available to your child/baby. Your doctor will explain the risks and benefits of these choices.

Please also note that specific treatment for HIV (that is anti-retroviral drugs like AZT) are NOT available in the public hospitals but can be bought privately.

What about confidentiality?

Efforts will be made to keep your child's/baby's personal information confidential, however we cannot guarantee absolute confidentiality. Your child's/baby's personal information may be disclosed if required by law. On our study record we will use codes instead of your child's/baby's name. Only the study staff will know these codes. The study workers will not give out any information about your child/baby without written consent from you. Your family's privacy will be respected. The public health authorities will be notified as usual if your child/baby has TB. Any publication of this study will not use your child's/baby's name or identify your child/baby personally.

Your child's/baby's study records may be inspected by the South African Department of Health, study staff, study monitors, and drug companies supporting this study. The study records will be kept separate from the normal medical records.

What are the costs to me?

There is no cost to you for the medication, study visits or laboratory tests. All medical care will be provided by the study doctor.

Will I receive any payment?

We will re-imburse you transportation money to enable you to attend the hospital or clinic.

What happens if my child/baby is injured?

If your child/baby is injured as a result of being in this study, your child/baby will be given immediate treatment for his/her injuries at no cost to you.

What are my rights and my child's rights as a research subject?

Participation in this study is completely voluntary. You may choose not to allow your child/baby to take part in this study or take your child/baby out of the study at any time. Your child/baby will be treated the same no matter what you decide, there will be no penalty.

We will tell you about new information from this or other studies that may affect your child's/baby's health, welfare or willingness to stay in this study. If you want the results of the study, let the study staff know

What do I do if I have questions or problems?

For questions about this study or a research-related injury, contact either:

Prof Peter Donald: **Tel**: 021/938-9506 **or** **Prof Gregory Hussey**: **Tel**: 021/685-4103

SIGNATURE PAGE

THE PHARMACOKINETICS AND TOXICITY OF ANTITUBERCULOSIS AGENTS AND OTHER CO-ADMINISTERED DRUGS IN CHILDREN, WITH AND WITHOUT HIV INFECTION AND THEIR RELATIONSHIP TO NUTRITIONAL STATE AND TO THE NAT2 ACETYLATOR GENOTYPE AND PHENOTYPE.

If you have read this consent form (or had it explained to you), all your questions have been answered and you agree to take part in this study, please sign your name below.

_____

Participant's Name (print)

_____ _____

Participant's Mother or Father Legal Guardian's Signature and Date

or Legal Guardian(As appropriate)(print)

_____ _____

Study Staff Conducting Study Staff Signature and Date

Consent Discussion (print)

_____ _____

Witness' Name (print) Witness's Signature and Date

Consent by a parent or legal guardian that the HIV status of their child may be determined.

Title of the study:

THE PHARMACOKINETICS AND TOXICITY OF ANTITUBERCULOSIS AGENTS AND OTHER CO-ADMINISTERED DRUGS IN CHILDREN, WITH AND WITHOUT HIV INFECTION AND THEIR RELATIONSHIP TO NUTRITIONAL STATE AND TO THE NAT2 ACETYLATOR GENOTYPE AND PHENOTYPE.

As explained in the patient information document it is uncertain whether it is necessary to treat children with HIV infection and tuberculosis for 6 months or 9 months. It is therefore important for the researchers to know whether or not your child is infected with the HI-virus. We therefore request your permission to allow us to determine the HIV status of your child. To do this a single sample of blood of about 2,5 ml, or half-a-teaspoonful, will be drawn by inserting a needle into one of the veins in your child's arm. You will be informed of the results of the test as soon as they become available. The results will be known only to the researchers who are conducting the study. When the results are available you will receive further counseling and should the result indicate that your child is HIV-infected you will be referred to the infectious diseases clinic for advice and further management.

Consent

I, the undersigned parent (or guardian) of (give name of child):_____
_____,

herewith give permission that the HIV-status of my child may be determined.

Signature of parent or legal guardian giving consent:_____
Parent or legal guardian's name in block letters:_____

Date:_____

Signature of witness confirming consent: _____
_____

Name of witness in block letters*:*_____

Date:_____

INGELIGTE TOESTEMMING

PEDIATRIESE HIV/TB NAVORSINGKONSORTIUM

UNIVERSITEIT VAN KAAPSTAD

EN

UNIVERSITEIT VAN STELLENBOSCH

DIE FARMAKOKINETIKA EN TOKSISITEIT VAN ANTITUBERKULOSE-MIDDELS EN ANDER SAAMTOEGEDIENDE MIDDELS IN KINDERS MET TUBERKULOSE MET OF SONDER MIV-INFEKSIE EN HULLE VERWANTSKAP MET DIE VOEDINGSTATUS EN DIE NAT2-ASETILATOR GENOTIPE EN FENOTIPE

Verkorte titel vir die studie: **Die farmakokinetika van antituberkulosemiddels in kinders met tuberkulose met en sonder MIV-infeksie.**

Inleiding

TB en MIV-infeksie is ernstige gemeenskapsgesondheid probleme in Suid Afrika. Wanneer hulle saam voorkom word die uitkoms van beide toestande slegter. Daar is ook onsekerheid oor wat is die beste dosisse van antituberkulose medisyne wat in kinders gegee behoort te word, beide in die met, en sonder MIV-infeksie. Aan die een kant mag te min medisyne onvoldoende wees om die tuberkulose kieme dood te maak en mag dus tot die opflikkering van tuberkulose lei; aan die anderkant mag te veel medisyne tot toksisiteit lei. Dit is ook moontlik dat kinders met MIV-infeksie meer vatbaar mag wees vir die toksiese newe-effekte van antituberkulose medisyne. Tydens hierdie studie sal ons die wyse waarop kinders antituberkulose medisyne absorbeer en verteer meet en kyk of MIV-infeksie en sy komplikasies, wanvoeding of tuberkulose self enige uitwerking het op die manier hoe kinders met tuberkulose antituberkulose middels absorbeer en daarop reageer.

Hierdie studie word deur Bristol-Myers Squibb – "*Secure the future"*-Stigting geborg.

Die geneeshere in beheer van die studie by hierdie lokaal is Professor Peter Donald van die Departement Pediatrie en Kindergesondheid van die Fakulteit Gesondheidswetenskappe, Universiteit van Stellenbosch en Professor Gregory Hussey van die Departement van Kinder- en Adolesente-gesondheid van die Fakulteit van Gesondheidswetenskappe van die Universiteit van Kaapstad.

Voordat u besluit of u wil hê dat u kind/baba moet deelneem aan die studie, wil ons eers graag hê dat u van die studie moet weet. U mag verkies dat u kind nie aan die studie deel neem nie. Geen gesondheidsorg sal vir u kind weerhou word nie al sou u besluit om nie aan die studue

deel te neem nie.U kind sal dan steeds die gewone TB-behandeling onvang wat by hierdie kliniek/hospitaal gebruik word.

Hierdie is ‘n toestemmingsvorm. Dit gee u inligting in verband met die studie. Die studiepersoneel sal met u gesels oor die inligting. Dit staan u vry om te eniger tyd vrae oor die studie te vra. Indien u instem dat u kind aan die studie mag deelneem, sal u gevra word om die toestemmingsvorm te teken. U sal ‘n afskrif kry wat u kan hou.

Hoekom word hierdie studie gedoen?

Die doel van hierdie studie is om die absorpsie van antituberkulose medisyne in kinders met tuberkulose, beide met, of sonder, MIV infeksie te bepaal. Ons sal ook nagaan of faktore soos wanvoeding, lewersiekte of die teenwoordigheid van tuberkulose kliere in die buik die absorpsie van antituberkulose middels, hulle toksisiteit of hulle vermoë om tuberkulose te genees, beïnvloed.

Wat sal met my kind gebeur en wat word van my verwag as my kind deelneem aan hierdie studie?

Sou u besluit om u kind aan hierdie studie te laat deelneem sal 'n aantal ondersoeke gedoen word. Hierdie ondersoeke sal vir ons help bepaal of u kind MIV-infeksie het, hoe ernstig die infeksie is, of hy/sy wangevoed is en of daar enige tekens van lewerskade is. Ons sal ook die funksie van die immuunsisteem nagaan deur sekere witselle in die bloed te tel. Die absorpsie van die antituberkulose medisyne sal bepaal word deur 'n naald in 'n aar te plaas en dan daardeur vierkeer 'n klein hoeveelheid bloed te neem. Die hoeveelheid medisyne in die bloed monsters sal dan bepaal word. Die toets sal na twee maande herhaal word om te kyk of 'n verbetering in voeding of die behandeling van tuberkulose enige verskil in die absorpsie van die middels te weeg gebring het. Al hierdie ondersoeke beteken dat daar om en by 3 teelepelsvol bloed van u kind geneem sal moet word.

'n X-straal ondersoek van die borskas en 'n spesiale ondersoek met klankgolwe van die buik sal ook gedoen word om die verspreiding van tuberkulose in die liggaam te beoordeel. U kind se stoelgang sal ook ondersoek word vir wurms en tekens van 'n swak vermoë om voedsel te absorbeer. Die uriene sal gereeld nagegaan word vir tekens van siekte.

Indien die diagnose van tuberkulose nog nie bevestig is nie, sal maagsappe en keel aspirate twee agerteenvolgende oggende getrek word om die tuberkulose kiem te probeer sien of kweek.

U kind sal ook een keer elke maand ondersoek word vir tekens van wanvoeding en u kind sal ook elke week vir tekens van toksisiteit as gevolg van die tuberkulose medisyne ondersoek word. Daar sal elke week vir die eerste maand van behandeling en maandeliks daarna, terwyl u kind in hospitaal behandel word, 'n bloedtoets gedoen word om moontlike lewerskade as gevolg van die tuberkulose behandeling vroegtydig op te spoor. Hierdie toets benodig ongeveer 'n halwe teelepelvol bloed.

Na 2 maande en 6 maande na toelating tot Brooklyn Hospitaal sal sekere van die bloed toetse herhaal word. Hierdie toetse sluit in dié vir die evaluasie van voeding, immuniteit en lewerskade. Ongeveer twee teelepels bloed word elke slag benodig vir hierdie toetse. Die X-straal ondersoek van die borskas sal 2 maande, 4, 6 en 18 maande na die begin van behandeling herhaal word.

Die klankgolf X-straal ondersoek van die buik sal 4 maande na die begin van behandeling herhaal word.

Na 6 maande van behandeling sal 'n maagsap en keel aspiraat weer verkry word en sal daar weer vir die tuberkulose kiem gesoek word om te bevestig dat u kind se tuberkulose werklik genees is.

Opvolg Besoeke

Na ontslag uit Brooklyn Hospitaal sal u 'n afspraak kry om u kind na die Tygerberg Kinderhospitaal of die Rooikruis Kinderhospitaal te bring 18 maande na die begin van tuberkulose behandeling. Tydens hierdie besoek sal die X-straal ondersoek van die borskas en die buik herhaal word as ook die bloed toetse om u kind se voeding en immuniteit te bepaal en ook om te kyk of daar enige tekens van lewerskade is. Hierdie toetse sal ook om en by twee teelepelsvol bloed benodig. 'n Stoelgang sal ook weer ondersoek word vir wurms en tekens van gebrekkige absorpsie van voedingstowwe.

Hoeveel kinders sal aan die studie deelneem?

Ongeveer 100 kinders sal aan die studie deelneem.

Hoe lank sal my kind/baba in die studie wees?

U kind sal in die studie wees vir 18 maande na die begin van tuberkulose behandeling. Indien moontlik sal ons u kind vir 'n verdere drie jaar wil opvolg, om enige langtermyn probleme wat verband mag hê met die behandeling van tuberkulose te identifiseer, maar ons besef dat dit dalk vir u moeilik sal wees..

Vir watter redes sal die dokter my kind/baba vroeër uit die studie haal?

Die studiedokter mag moontlik u kind/baba vroeër uit die studie verwyder sonder u toestemming as:

- Die studie deur die Etiese Komitee (die komitee wat toesig hou oor die veiligheid en regte van die studiepasiënte) gekanselleer word.
- ‘n Dataveiligheid Toesighoudende Raad (DVTR) aanbeveel dat die studie vroegtydig gestaak moet word. (Die DVTR is ‘n buitegroep van kundiges wat die studie dophou).
- U kind/baba nie die studiebesoeke kan nakom soos deur die studie verlang nie.
- Die studiedokter besluit dat dit vir u kind/baba skadelik is om met die studie voort te gaan.

- **Wat is die risiko’s van die studie?**

  Newe-effekte (nadelige gevolge) op TB-behandeling is relatief skaars, maar dit kan erg wees in sommige pasiënte. Indien u kind/baba enige vorm van die newe-effekte hieronder beskryf, ervaar, moet u die studiedokter of studieverpleegkundige onmiddellik laat weet.

Die newe-effekte van die TB-medikasie wat u aan die studiedokter of studieverpleegkundige moet rapporteer is:

Veluitslag, vae of veranderde visie (oë kyk snaaks), griepagtige simptome en koors vir meer as 3 dae, maagpyne en diaree, naarheid en braking, verlies aan eetlus, gewrigspyne (pyne in litte), kneusplekke, duiseligheid, speldprikgevoel en verlies van gevoel om die mond, naalde-en-spelde gevoel in die hande en voete. Een van die anti-TB-middels wat u kind/baba gaan kry, rifampisien, gaan die uriene, sweet en trane ‘n oranje kleur gee.

- **Is daar voordele om deel te neem aan die studie?**

As u kind/baba aan die studie deelneem, kan daar ‘n direkte voordeel vir u kind/baba wees, maar geen waarborg kan hiervoorgegee word nie. Dit is ook moontlik dat u kind/baba geen voordeel van deelname aan die studie sal hê nie. Inligting wat met die doen van hierdie studie verkry word, kan ander kinders en babas wat MIV- en TB-infeksie, of net TB sonder MIV-infeksie het, help.

- **Watter ander keuses behalwe hierdie studie is vir my kind/baba beskikbaar?**

In plaas daarvan om aan hierdie studie aan hierdie studie deel te neem, het u die keuse van TB-behandeling vir u kind/baba wat by hierdie hospitaal/kliniek beskikbaar is. Praat asseblief met u dokter oor hierdie en ander keuses wat vir u kind/baba beskikbaar is. U dokter sal die voor- en nadele van hierdie keuses aan u verduidelik.

Let asseblief ook daarop dat spesifieke behandeling vir MIV (dit is anti-retroviralemiddels soos AZT) tans *nie* in die staatshospitale beskikbaar is *nie*, maar wel privaat aangekoop kan word.

- **Wat van vertroulikheid?**

Ons sal moeite doen om u kind/baba se persoonlike inligting vertroulik te hou, maar ons kan nie absolute vertroulikheid waarborg nie. U kind/baba se persoonlike inligting kan geopenbaar word as die wet dit vereis. Op ons studierekords sal ons kodes gebruik in plek van u kind/baba se naam. Slegs die studiepersoneel sal hierdie kodes ken. Dit studiepersoneel sal geen inligting oor u kind/baba verstrek sonder u skriftelike toestemming nie. U gesin se privaatheid sal gerespekteer word. Die gemeenskapsgesondheids-owerhede sal, soos gebruiklik, in kennis gestel word indien u

kind/baba TB het. Enige publikasie voortspruitend uit hierdie studie sal nie die naam van u kind/baba verstrek nie, of u kind/baba persoonlik identifiseer nie.

U kind/baba se studierekords kan deur die Suid-Afrikaanse Departement van Gesondheid, studiepersoneel, studiemoniteerders en farmaseutiese firmas wat die studie finansieel ondersteun, ondersoek word. Die studierekords sal apart van die normale mediese lêers gebêre word.

- **Wat sal dit my kos?**

Daar is geen koste vir u ten opsigte van die medikasie, studiebesoeke of laboratoriumondersoeke nie. Alle mediese sorg sal deur die studiedokter voorsien word.

- **Sal ek enige betaling ontvang?**

Ons sal u vervoerkoste aan u terugbetaal om dit vir u moontlik te maak om die hospitaal/kliniek by te woon.

- **Wat gebeur as my kind/baba beseer word**

Indien u kind/baba beseer word as gevolg van deelname aan die studie, sal u kind/baba onmiddelike behandeling vir sy/haar besering ontvang.

- **Wat is my regte en my kind/baba se regte as 'n navorsingonderwerp?**

Deelname aan die studie is heeltemal vrywillig. U mag kies om nie u kind/baba aan die studie te laat deelneem nie, of u kind/baba te eniger tyd uit die studie te onttrek. U kind/baba sal dieselfde behandeling ontvang, dit maak nie saak wat u sou besluit – daar sal geen straf wees nie.

Ons sal vir u op hoogte hou van enige nuwe informasie vanuit hierdie of ander studies wat u kind/baba se gesondheid mag affekteer of u bereidwilligheid om nog deel te neem aan hierdie studie. Indien u belangstel in die uitslae van hierdie studie stel asseblief vir die studie personeel in kennis.

Wat moet ek maak as ek vrae of probleme het?

In verband met vrae ten opsigte van die studie of 'n navorsingsverwante beseering bel vir **Prof PR DonaldTel: 021/9589506** of **Prof G Hussey: tel: 021/685-4103**

HANDTEKENINGBLADSY

DIE FARMAKOKINETIKA EN TOKSISITEIT VAN ANTITUBERKULOSE-MIDDELS EN ANDER SAAMTOEGEDIENDE MIDDELS IN KINDERS MET TUBERKULOSE MET OF SONDER MIV-INFEKSIE EN HULLE VERWANTSKAP MET DIE VOEDINGSTATUS EN DIE NAT2-ASETILATOR GENOTIPE EN FENOTIPE

As u hierdie toestemmingsvorm gelees het (of dit aan u verduidelik is), al u vrae beantwoord is en u instem om deel te neem aan die program, teken asseblief u naam hieronder .

_____

Deelnemer se naam(drukskrif)

_____ _____

Deelnemer se Moeder, Vader of Wettige Voog(soos Toepaslik) in drukskrif

Wettige Voog se handtekening

Datum ……..

_____ _____

Studie Personeel wat Toestemmings Bespreking Behartig (drukskrif)

Studie Personeel se Handtekening

Datum……..

_____ _____

Getuie se Naam(drukskrif) Getuie se Handtekening

Datum……

Toestemming deur ’n ouer of wettige voog dat die MIV-status van hulle kind bepaal mag word.

Titel van die studie: DIE FARMAKOKINETIKA EN TOKSISITEIT VAN ANTITUBERKULOSE-MIDDELS EN ANDER SAAMTOEGEDIENDE MIDDELS IN KINDERS MET TUBERKULOSE MET OF SONDER MIV-INFEKSIE EN HULLE VERWANTSKAP MET DIE VOEDINGSTATUS EN DIE NAT2-ASETILATOR GENOTIPE EN FENOTIPE

Soos in die pasiënt informasie dokument verduidelik, is dit onseker of kinders met MIV-infeksie en tuberkulose vir 6 maande of 9 maande behandel moet word. Dit is dus belangrik vir die navorsers om te weet of u kind met die MI-virus geïnfekteer is al dan nie. Ons versoek dus u toestemming om ons toe te laat om u kind se MIV-status te bepaal. Om dit te doen moet ’n enkele bloedmonster van 2,5 ml, of omtrent ’n halwe teelepel vol, geneem word deur ’n naald in een van die are in u kind se arm te plaas. U sal ingelig word oor die uitslag van die toets sodra dit beskikbaar word. Die uitslag sal slegs bekend wees aan die navorsers verantwoordelik vir die uitvoering van die studie. Beide voor en na die toets sal u toepaslike berading ontvang en indien die uitslag van die studie daarop sou dui dat u kind met die MIV geinfekteer is, sal u verwys word na die Infeksie Siekte Kliniek vir raad en hulp.

Toestemming

Ek, die ondergetekende ouer (of wettige voog) van (gee naam van die kind):

---------- gee hiermee toestemming dat die MIV-status van my kind bepaal mag word.

Handtekening van die ouer of wettige voog wat toestemming gee:

Naam van ouer of voog in blokletters: **----------**

Datum: **----------**

Handtekening van getuie wat die toestemming bevestig:

Naam van getuie in blokletters: **----------**

Datum: **----------**

Pharmacokinetic study Xhosa consent form:Version 2

BMS: Khusela Ixesha Elizayo

INtlangano yamaQumrhu oPhando ngesifo sephepha (TB) ne-HIV ebantwaneni

IYunivesithi yaseKapa / iYunivesithi yaseStellenbosch

THE PHARMACOKINETICS AND TOXICITY OF ANTITUBERCULOSIS AGENTS AND OTHER CO-ADMINISTERED DRUGS IN CHILDREN, WITH AND WITHOUT HIV INFECTION AND THEIR RELATIONSHIP TO NUTRITIONAL STATE AND TO THE NAT2 ACETYLATOR GENOTYPE AND PHENOTYPE.

Isihloko esifutshane: I-pharmacokinetics kunye netyhefu eyenziwa sisifo sephepha ebantwaneni abanayo nabangenayo i-HIV.

Amaxwebhu eMvume yolwazi

Intshayelelo

I-HIV/AIDS kunye nesifo sephepha zezona zifo eziyigxaki yempilo e-Mzantsi Afrika. Xa ezi zifo zivela zombini zenzelana isiphumo esibi kumntu ogulayo. Akuqinisekwanga ukuba leliphi iyeza elinganceda kakhulu kulawo akhoyo okunyanga isifo sephepha (antituberculosis medicines), angasetyenziswa ebantwaneni abanesifo sephepha, nabo abanayo nabangenayo i-HIV. Kwelinye icala kungenzeka ukuba xa ulisebenzisa kancinci eli yeza lingathi lingoneli ekubulaleni intsholongwane yesifo sephepha, lonto ingenza ukuba isifo sephepha singapheli emzimbeni; kwelinye icala xa ulisebenzisa kakhulu eli yeza lingenza ubenetyhefu emzimbeni. Kungenzeka ukuba abantwana abaphethwe yi-HIV bangabasengozini yetyhefu eyenziwa sisiphumo esisesinye ngaphandle kweso besijongiwe ngenxa yamayeza anyanga isifo sephepha (antituberculosis medicines). Ngexesha lesi sifundo sizakwenza umlinganiselo wendlela abantwana abaphethwe sisifo sephepha abathi baphatheke ngayo nenguqulelo emizimbeni yabo ngala mayeza okunyanga isifo sephepha kwakunye nokuvavanya i- HIV nokungatyi kakuhle kunye nesifo sephepha, bafumana eziphi iziphumo ezingezinye ngaphandle kwezo bezijongiwe ngenxa yamayeza e-TB.

Esi sifundo sixhaswe ngemali ngabakwa Bristol Myers Squibb – Secure the Future Foundation.

OoGqirha abaphetheyo kwesi sifundo kule ndawo ngaba: Professor Peter Donald of theDepartment of Paediatrics and Child Health of the Faculty of Health Sciences, the University of Stellenbosch and Professor Gregory Hussey of the School of Child and Adolescent Health. University of Cape Town.

Ngaphambi kokuba uvumele umntwana wakho ukuba athathe inxaxheba kwesi sifundo, sifuna ukukwazisa ngesi sifundo sisonke. Kuxhomekeke kuwe ukuba uyafuna okanye awufuni ukuthatha inxaxheba kuso. Akusayi kurhoxiswa lunyango kumntwana wakho xa ungafuni ukuthatha inxaxheba kwesi sifundo. Umntwana wakho uza kukwazi ukuya eklinikhi okanye esibhedlele ukuze afumane unyango lwesifo sephepha (TB).

Lena yifomu yesivumelwano. Ikunika ulwazi ngesi sifundo. Iqela labasebenzi kolu fundo baza kuthetha nawe ngolwazi nangezinto ofuna ukuzazi. Ungabuza noba yintoni, noba kunini ukuba awuqinisekanga ngesi sifundo. Ukuba uyavuma ukuba umntwana wakho athathe inxaxheba

kwesi sifundo, uzakucelwa ukuba usayine ifomu yesivumelwano. Uzakufumana ikopi oza kuyigcina.

Kutheni kusenziwa esi sifundo?

Injongo yesi sifundo kukuvavanya ukuthabatheka okanye indlela athi asebenze ngayo amayeza okunyanga isifo sephepha ebantwaneni abaphethwe sesi sifo, nabaphethwe yintsholongwane eyosulelayo i-HIV. Siya kuphinda sihlole iimeko ezifana nokungabinako ukutya okwaneleyo okunempilo okanye ukungondleki, isifo sesibindi okanye ubukho besifo sephepha buthi buchaphazele ukutsaleka kwamayeza esifo sephepha, ubutyhefu bawo okanye indlela athi akwazi ngayo ukunyanga isifo sephepha.

Kuzakwenzeka ntoni emntwaneni wam, yintoni ekufanele ndiyenze xa umntwana ekwesi sifundo?

Ukuba ugqibe ekubeni umntwana wakho makathathe inxaxheba kwesi sifundo, kuza kwenziwa uluhlu lophando. Olu phando luza kusinceda ukubona ukuba umntwana wakho akanayo na i-HIV, nokubona ukuba isifo simphethe kangakanani, okanye akondlekanga, kwakunye nokuba kukho iimpawu zesibindi esonakeleyo. Siza kubala inani leeseli ezimhlophe egazini ukwenzela ukuvavanya obungakanani bomlinganiselo asebenza ngayo amajoni omzimba. Kuza kwenziwa isifundo ngokufunxwa kwamayeza anyanga isifo sephepha ngokufaka inaliti kumthambo wegazi, kutsalwe amaqabaza egazi kahlanu kwixhesha ngalinye kolu phando lubini. Kuza kubalwa inani leyeza eliphakathi egazini. Olu vavanyo luza kuphindwa emva kwenyanga ezine emva konyango lokuqala lwesifo sephepha ukwenzela ukubona ukuba awukho na umahluko obhetele kwisondlo, nokuba isifo sephepha senze umahluko omngakanani ngeli xesha iyeza lisebenza emzimbeni. Lonke olu phando olungentla olwenziweyo luchaza ukuba kuza igazi 4-elingangeetisipuni ezintathu kumntwana wakho.

Kuza kuthathwa i-X-rayi yesifuba kunye ne-X-rayi yodwa yesisu ukuvavanya ukuba isifo sephepha singene kangakanani emzimbeni. Ituwa yomntwana wakho izakuhlolwa kukhangelwe impawu zeenthsulube kunye nokubona ukuba ukutya kutsaleka kakuhle na okanye akutsaleki okanye amayeza isifo sephepha ayatsaleka emzimbeni. Umchamo uza kuhlolwa rhoqo ukujonga impawu zesifo.

Ukuba uxilongo lwesifo sephepha alubonakali kuza kutsalwa incindi yesisu ngethumbu rhoqo kusasa intsuku zilandelelana, ukuzama ukhulisa, okanye ukubona intsholongwane yesifo sephepha.

Umntwana wakho uzakuhlolwa rhoqo ngenyanga impawu zokuba utya kakuhle na, aphinde ahlolwe rhoqo ngeveki impawu zetyhefu eyenziwa ngamayeza esifo sephepha, kuphindwe kuhlolwe igazi ukwenzela ukubona ukuba isibindi sonakale kangakanani xa kunyangwa isifo sephepha kanye ngeveki, kwinyanga yokuqala, emva koko anganyangwa kubekanye ngenyanga ade akhutswe esibhedlele. Kolu vavanyo kufuneka ihafu yetisipuni yegazi.

Emva kwenyanga ezine efikile esibhedlele sase-Brooklyn, ukuhlolwa kwegazi kuzakuphindwa. Oku kuquka uvavanyo lwendlela yokutya, ukungabinakusulelwa kwakho zizifo ezithile nokonakalelwa sisibindi. Kolu luvavanyo kufuneka itisipuni ezimbini zegazi. Ufundo lwe-X-ray yesifuba luza kuphindwa kwiinyanga ezimbini, ezine, ezintandathu emva kokuqalisa unyango lwesifo sephepha. I-X-rayi yesisu iza kuphindwa kwiinyanga ezine emva kokuqalisa unyango lwesifo sephepha.

Emva kwenyanga ezimbini unyango lwencindi zesisu luza kuphindwa lenziwe ukuqinisekisa ukuba umntwana wakho unyangekile kwisifo sephepha.

Olu fundo luza kwenziwa ngabantwana abangaphi ?

Kuza kubhaliswa abantwana abangama-80 kwesi sifundo.

Uzakuthatha ixesha elingakanani umntwana wakho ekwesi sifundo?

Umntwana wakho uzakuhlala ixesha elingangeenyanga ezisithandathu emva kokuba eqalile unyango lwesifo sephepha.

Kutheni ugqirha eza kuthatha umntwana wam/usana lwam aluyekise kolu fundo kamsinyane?

UGqirha wesi sifundo angakhawuleza amyekise umntwana wakho kolu fundo ngaphandle kwemvume yakho xa:

Ufundo luyekiswe yiKomiti ebizwa ngokuba yi-Ethics Committee (ikomiti ejonga ukhuseleko namalungelo ophando kwisifundo).

I-Data Safety Monitoring Board (DSMB) iphakamise uluvo lokuba olu fundo luyekiswe kwangethuba (I-DSMB liqela langaphandle leengcaphephe ezongamele isifundo esithile).

Umntwana wakho/ usana lwakho alukwazi ukufikelela kolufundo ngemini abizwe ngazo njengoko kufuneka njalo.

Ugqirha wesifundo ubona ukuba umntwana wakho usengozini kolu fundo.

Zeziphi iingozi kolu fundo?

Ububi obenziwa ngamayeza okunyanga i-TB bunqabile kodwa kwezinye izigulane kungaphuma iziphumo ezibi. Ukuba umntwana wakho ufumana isiphumo esisesinye ngaphandle kweso besijongiwe nezichaziweyo ngezantsi, kufuneka wazise ugqirha wesifundo okanye umongikazi ngokukhawuleza

Iziphumo ezizezinye ngaphandle kwezo bezijongiwe zokunyanga i-TB ezichaziweyo ngezantsi, kufuneka wazise ugqirha wesifundo okanye umongikazi wesifundo ngokukhawuleza: irhashalala, ukubona mfiliba okanye ukungaboni ngale ndlela obubona ngayo ekuqaleni, iimpawu zefiva nokuba nefiva ngaphezu kweentsuku ezintathu, ukuphathwa sisisu okanye isisu esixuxuzelayo, isicaphucaphu, ukugabha, ukungacaceli ukutya, amalungu omzimba abuhlungu, ukugruzuka, isiyezi, ukuntlontlozela kunye nobundindisholo obujikeleze umlomo, ukuntlontlozela okuvakalayo ezandleni nasezinyaweni. Esinye seziyobisi ze-TB, i-Rifampicin, eza kunikwa umntwana wakho, iza kutshintsha umbala womchamo, wombilo kunye nenyembezi zibe-orenji.

Ikhona na inzuzo efumanekayo kolu fundo?

Ukuba umntwana wakho uthatha inxaxheba kolu fundo, umntwana wakho kungenzeka afumane uncedo olukhulu, kodwa oku akunakuqinisekiswa. Kungenzeka ukuba umntwana wakho angafumani nto ngokuthatha kwakhe inxaxheba kwesi sifundo. Ulwazi olufumaneke kwesi sifundo lunganceda abanye abantwana neentsana ezine-HIV kunye ne-TB okanye abane-TB kodwa bengenayo i-HIV.

Zeziphi ezinye izinto umntwana wam anokuzikhethela zona ngaphandle kolu fundo?

Endaweni yokuthatha inxaxheba kolu fundo, umntwana wakho angakwazi ukufumana uncedo lokunyanga i-TB eklinikhi okanye esibhedlele. Uyacelwa ukuba uthethe nogqirha wakho malunga noku kunye nezinto ongazenzayo ekuncedeni umntwana wakho. Ugqirha wakho uyakuchazela kakuhle ngobungozi kunye nenzuzo ongayifumana kwesi sifundo

Nceda uqaphele ukuba unyango olujongene ne-HIV (i-anti-retroviral drugs enjenge- AZT) ayifumaneki ezibhedlela zoluntu kodwa ungakwazi ukuyithenga kwindawo zabucala zonyango.

Ingaba oku kugcinwa kulihlebo?

Kuya kwenziwa iinzame zokugcina ulwazi ngomntwana wakho luyimfihlo, kodwa asinokuqinisekisa ngokufihla olu lwazi Ulwazi ngomntwana wakho luya kuvezwa xa lifunwa ngabomthetho. Kwesi sifundo siza kusebenzisa iikhowudi endaweni legama lomntwana wakho. Ezi khowudi ziya kwaziwa ngabasebenzi abakolufundo kuphela. Abantu abasebenza kwesi sifundo abanalungelo lokunika ulwazi olumalunga nomntwana wakho ngaphandle kwemvume yakho ebhalwe phantsi. Imfihlo yosapho lwakho ihloniphekile. Iziphatha-mandla zempilo yoluntu ziya kwaziswa njengendlela eqhelekileyo ukuba umntwana wakho une-TB. Upapasho lwesi sifundo alusayi kusebenzisa igama lomntwana wakho okanye kukhethwe umntwana/ usana lwakho ngenkqu.

Iingxelo zomntwana/zosana lwakho ziyakuhlolwa liSebe loMzantsi Afrika lezeMpilo, abasebenzi kolu fundo, omnye umntu okwesi sifundo onikwe igunya lokuphatha abanye, kunye neenkampani zeziyobisi ezixhase olu fundo. Iingxelo zesi sifundo ziya kugcinwa ngokwahlukeneyo kwiingxelo eziqhelekileyo zonyango.

Ndiza kuhlawula imali engakanani?

Ayikho imali ozakuyihlawula xa usiza kwesi sifundo, kunye namayeza okanye nohlolo olwenziwa kwindlu esetyenziswa ekwenzeni uphando nemilingo yeenzululwazi. Lonke unyango luya kunikezwa ngugqirha wesifundo.

Ingaba ukhona umvuzo endizakuwufumana?

Imali yesithuthi oyisebenzisileyo xa usiza eklinikhi okanye esibhedlele siza kuyibuyisa.

Kuza kwenzeka ntoni xa umntwana wam/usana lwam lonzakele?

Ukuba umntwana/ usana lwakho lwenzakele ekule nkqubo yesi sifundo, uya kufumana unyango olukhawulezileyo ngaphandle kwentlawulo.

Ngawaphi amalungelo endinawo mna kunye nomntwana wam ngokuthatha inxaxheba kwesi sifundo?

Ukuthatha inxaxheba kwesi sifundo ukwenza ngokuzithandela kwentliziyo yakho. Ungangamvumeli umntwana wakho ukuba athathe inxaxheba kolu fundo, okanye ungamkhupha nokuba kunini umntwana wakho kolu fundo. Umntwana/ usana lwakho luya kufumana unyango olufanayo, nokuba ufike kwesiphi isigqibo, akusayi kubakho sohlwayo.

Sizokuxelela xa kukhona ulwazi olutsha olufikileyo, nolunye ufundo olunesiphumo esifana nesi olungaphazamisa impilo yomntwana wakho, ezentlalo-ntle okanye ukuvuma ukusebenzisana kwesi sifundo. Xa ufuna iziphumo zesi sifundo, kufuneka wazise abasebenzi kwesi sifundo.

Ndenze ntoni xa ndinemibuzo okanye iingxaki?

Mayelana nemibuzo ngesi sifundo okanye uphando malunga nokwenzakala, dibana no:

Prof Peter Donald: **Ifoni**: **(**021) 938-9506 **okanye Prof Gregory Hussey**: **Ifoni**: (021) 685-4103

IPHEPHA LOKUSAYINA

THE PHARMACOKINETICS AND TOXICITY OF ANTITUBERCULOSIS AGENTS AND OTHER CO-ADMINISTERED DRUGS IN CHILDREN, WITHAND WITHOUT HIV INFECTION AND THEIR RELATIONSHIP TO NUTRITIONAL STATE AND TO THE NAT2 ACETYLATOR GENOTYPE AND PHENOTYPE.

Ukuba uyifundile le fomu yesivumelwano (okanye ucaciseliwe okuqhubekayo kule fomu), yonke imibuzo yakho iphenduliwe kwaye uyavuma ukuthatha inxaxheba kwesi sifundo, nceda usayine igama lakho ngezantsi.

_____

Igama loMthath'inxaxheba (bhala ngonoobumba abangadityaniswanga)

_____

Igama likaMama okanye likaTata womthathi-nxaxheba okanye Umgcini Osemthethweni (Ngokubekiweyo)

Umgcini Osemthethweni Sayina kunye Nomhla

(bhala ngonoobumba abangadityaniswanga)

_____

Umsebenzi oQhuba uFundo msebenzi okolu fundo: Sayina kunye nomhla

Imvume yengxoxo (bhala ngonoobumba abangadityaniswanga)

_____

Igama lengqina Isandla sengqina nomhla

Imvume eyenziwa ngumzali okanye umgcini womntwana ngokusemthethweni malunga nokwaziswa kobume be-HIV emntwaneni wabo.

Isihloko sofundo:

THE PHARMACOKINETICS AND TOXICITY OF ANTITUBERCULOSIS AGENTS AND OTHER CO-ADMINISTERED DRUGS IN CHILDREN, WITH AND WITHOUT HIV INFECTION AND THEIR RELATIONSHIP TO NUTRITIONAL STATE AND TO THE NAT2 ACETYLATOR GENOTYPE AND PHENOTYPE.

Njengoba bekuchaziwe encwadini yolwazi yesigulana ukuba akuqinisekwanga ukuba ikhona na imfuneko yokunyanga umntwana one-HIV kunye nesifo sephepha ixesha elingangeenyanga ezintandathu okanye ezilithoba. Kubalulekile ukuba abaphandi baqinisekise ukuba umntwana wakho akanayo okanye unayo intsholongwane ye-HIV Ngenxa yoko, siyakucela ukuba usinike imvume sibone imeko ye-HIV emntwaneni wakho. Sizakutsala ngenaliti igazi elingumlinganiselo ongange-2,5 ml okanye ihafu yetisipuni egcweleyo kumthambo wegazi osengalweni yomntwana wakho. Uya kunikwa iziphumo zokuhlolwa xa sezikhona. Iziphumo ziya kwaziwa ngumphandi yedwa oqhuba olu fundo. Xa sezikhona iziphumo uzakufumana uncedo ukuba iziphumo zithi umntwana wakho une-HIV uya kuthunyelwa kwiklinikhi yezifo ezosulelayo ukuze ufumane iingcebiso nolawulo olungolunye loku.

Imvume

Mna, mzali osayine ngezantsi (okunye umgcini womntwana) ka- (bhala igama lomntwana):____

_____

Ndinikeza imvume yokujongwa kobume be-HIV emntwaneni wam.

Isandla somzali okanye umgcini womntwana onikeza imvume:

_____

Igama lomzali okanye umgcini womntwana ngoonobumba abakhulu:

_____

Umhla:_____-

Isandla sengqinga elingqinisisa imvume:_____

Umhla:_____

Igama lengqinga ngoonobumba abakhulu:_____

Appendix 2: 24-Hour-recall

	FOOD ITEMS	QUANTITY(g/ml)	BR	IS	L	IS	D	AD
TEA & COFFEE	Tea	Cup=180ml; mug=250ml						
	Coffee							
	+sugar; syrup; honey	1t sugar=6g; 1t honey/syrup=15g						
	+condensed milk	1t=10g						
	+evaporated milk	1t=3g						
	+non-dairy creamer	1t=4g						
	+WM powder	1t=4g						
	+milk: SM; WM; 2%; soy; breast	Med portions: 20ml-tea in cup 35ml-tea in mug 40ml-coffee in cup 75ml-coffee in mug						
	Other (specify)							
MILK & MILK DRINKS	Buttermilk	S/s=175ml; l/s=500ml; ½c=125g						
	Maas/sourmilk							
	Custard	S/s=350ml						
	Milk: SM; WM; 2%; soy; breast	To drink: ½c=125ml						
	Formula (specify) No of scoops/bot	Baby bottle=250ml						
	Yoghurt	S/s=175ml; yogisip=350ml; ½c=125g						
	Flavoured milk	Carton=250ml; s/s plastic=350ml						
DRINKS	Fruit juice-specify	Liquifruit s/s=250ml; Ceres s/s=200ml; cartons/bottles s/s=350ml, l/s=500ml						
	Cold drinks: squash; carbonated; diet	S/s bottle=350ml; l/s bottle=500ml; s/s can=340ml						
BREAKFAST	Maltabella: soft	½c=125g						

	M/Meal: soft; stiff; crumbly	1 c soft=250g; 1 c stiff=250g; 1c crumbly=140g						
	Oats; tastee wheat	½c=125g						
	Corn flakes	1c=40g						
	Honey crunch; muesli	½c=65g						
	Pronutro	½c=50g						
	Puffed wheat	½c=12g						
	Fruit loops	½c=18g						
	Special K; All Bran	½c=25g						
	Rice crispies	½c=20g						
	Weetbix	1=25g						
	+fat: B; HM, Med; PM	1t=5g						
	+sugar; syrup; honey	1t sugar=6g; 1t honey/syrup=15g						
	+condensed milk	1t=10g						
	+evaporated milk	1t=3g						
	+non-dairy creamer	1t=4g						
	+WM powder	1t=4g						
	+milk: SM; WM; 2%; soy; breast	125g-instant cereal 60g-porridge 180g-pronutro						
BREAD	Bread/rolls: Wh; Br; Ww	Wh+BR 10mm=30g; Ww 10mm=35g						
	Cream crackers; Provita; Tuc; Crackers Ww	CrCr=8g; Tuc=4g; Provita=6g						
	Muffins; scones	6cm diam=35g; 8cm diam=60g						
	Rusks	Comm=15g; other 30g						
SPREADS ON BREAD	Butter; Marg: HM ;med, PM	Thin=5g; Med=7g; Thick=10g						
	Fishpaste; Liver spread; meat paste	Thin=5g; Med=7g; Thick=10g						
	Jam; honey; syrup	Thin=10g; Med=20g; Thick=35g						
	Marmite; meat spread	Thin=2g; Med=4g; Thick=7g						

	Peanutbutter; sandwich spread; cheese spread	Thin=5g; Med=10g; Thick=20g						
	Eggs	1 egg=50g						
CHEESE	Cheddar; gouda	Grated: med=40g; cubes=30g; slice=8g						
	Cottage cheese; cream cheese	Med=20g; thick=30g						
	Macaroni cheese	1T=45g; 1SP=90g; ½c=115g						
MEAT	Bacon	1 rasher=10g						
	Beef; Bully beef	138x85x3=20g; ½c=100g						
	Mince	1T=40g; 1SP=65g;½c=100 g						
	Roast	120x60x5=35g						
	Steak	S/s 130x70x15=125g; L/s 165x70x20=270g						
	Stew, vegetables	1SP= 105g; ½c=125g						
	Chicken, +skin; skin	Breast=125g; thigh=80g; drumstick=42g; foot=30g; wing=30g						
	Chicken pie	Comm.=150g, home=90g						
	Chicken stew	1SP=90g; ½c=125g						
	Heart: beef; sheep	Sheep heart=50g; sheep kidney=30g; beef kidney=85g						
	Kidney: beef; sheep							
	Lung: beef							
	Lasagne	1T=40g; 1SP=75g; ½c=120g						
	Liver	Sheep=55g; chicken=30g; beef=80g						
	Mutton chop	Louin chop=60g; rib chop=40g						
	Polony	Comm slice=16g						

	Pork	Chop:115x80x20 =100g Roast:110x65x5= 30g 3 ribs=130g						
	Samoosa; meat; veg	S/s=42g						
	Sausage beef; pork	Beef:thinx200mm =45g; thickx165mm=90 g Pork med=55g						
	Spaghetti bolognaise	1T=40g;1SP=75g ; ½c=100g						
	Toppers/imana, cooked	1SP=85g; ½c=120g						
FISH	Fish	Small=50x55x30= 60g; med 100x55x30=120g; stew 1SP=95g; ½c=140g						
	Fish cakes	65x15mm=50g						
	Fish fingers	85mm=35g						
	Pilchards	1=75g						
	Sardines	S/s=7g; l/s=25g						
	Tuna	1/3c=50g						
STARCH	M/Meal: soft; stiff; crumbly	Stiff & soft: 1T=75g; 1SP=120g; ½c=125g Crum: 1T=30g; 1SP=75g; ½c=70g						
	Samp	1T=55g; 1SP=125g; ½c=125g						
	Rice	1T=25g; 1SP=60g; ½c=65g						
	Pasta (cooked)	1T=35g; 1SP=70g; ½c=90g						
	Spaghetti & tomato sauce	1T=45g; 1SP=80g; ½c=125g						
	Stamped wheat	1T=30g; 1SP=80g; ½c=80g						
	+B; HM; Med; PM; SO	1t=5g						

SOUPS & LEGUMES	Baked beans	1T=50g; 1SP=105g; ½c=135g						
	Beans (cooked)	1T=50g; 1SP=85g; ½c=135g						
	Breyani	1T=40g; 1SP=80g; ½c=85g						
	Lentils (cooked)	1T=40g; 1SP=80g; ½c=90g						
	Samp & beans	1T=50g; 1SP=125g; ½c=125g						
	Soup-packets	½c=125g						
	Homemade(specify)	1T=35g; 1SP=80g; ½c=130g						
	Sousboontjies	1T=40g; 1SP=105g; ½c=135g						
	Beanstew	1T=60g; 1SP=120g; ½c=125g						
VEGETABLES	Vegetables-Specify							
	Salad-specify							
	Potato	S/s=60g; m/s=90g						
	Potato mash	1T=50g; 1SP=115g; ½c=125g						
FR	Fruit-specify							
EXTRA	Pudding-specify							
	Cake+tart-specify							
	Sweets-specify							
INFANT FOODS	Baby cereals(dry): Nestum1;2;rice& maize Purity:mixed;w/w;rice Cerelac	1t=2g; 1T=8g; ½c=20g						
	+sugar; syrup; honey	1t sugar=6g; 1t honey/syrup=15g						

	+milk: SM; WM; 2%; soy; breast	125g-instant cereal 60g-porridge 180g-pronutro						
	First food fruit; veg	Jar=80g; 1t=11g						
	Fruit juice	½c=125ml						
	Infant dinners(dry): beef&veg; chicken& veg; guava& custard; mi veg; orange & banana	1t=5g; 1T=15g; ½c=47g						
	Junior food(jar): veg& meat; mix veg; pasta &beef	Jar=200g; 1t=11g; ½c=125g						
	Junior fruit (jar)							
	Junior pudding							
	Strained food(jar): macaroni beef; veg &meat; fruit& yoghurt; fruit; pudding; vegetables	Jar=125g; 1t=11g; ½c=125g						
OTHER								

Appendix 3: Food frequency questionnaire

The intake during the past six months by the child and during the past 6 months for babies younger than 1 year.

	FOOD	DESCRIPTION	QUANTITY (g/ml)	AMOUNT USUALLY EATEN (HHM)	AMOUNT USUALLY EATEN (g)	P/D	D/W	P/M	SELDOM/ NEVER
PORRIDGE	Maize-meal porridge	Stiff	1c=250 g 1T=75g						
		Soft	1c=250 g 1T=75g						
		Crumbly	1c=140 g 1T=30g						
	Maltabella porridge		½c=125 g						
	Oats porridge		½c=125 g						
	Other cooked cereal	Specify type:							
	Milk on porridge	None							
		Full cream	Little= 30g Med= 60g Much= 125g						
		Sour							
		2%							
		Fat free/ skim							
		Milk blend							
		Soy milk							
		Condensed	1t= 10g						
		Evaporated	1t= 3g						
		Non-dairy creamer	1t= 4g						
	Is sugar added to porridge?	None							
		White	1t= 6g						
		Brown							
		Syrup	1t= 15g						

		Honey							
	Is fat added to porridge?	None							
		Butter	1t= 5g						
		Hard margarine							
		Soft margarine (PM)							
		Soft margarine (Med)							
		Oil							
		Peanut butter	1t= 12g						
BREAKFAST CEREAL	Breakfast cereals	Specify types usually eaten							
	Baby/ infant cereals	Specify type usually used	1t= 2g 1T= 8g ½c= 20g						
	Milk on cereal	Specify type							
	Is sugar added to cereal?	Specify type							
	Is fat added to cereal	Specify type							
STARCHES	Samp		1T= 55g 1 SP= 125g ½c= 125g						
	Samp and beans	Ratio							
	Rice	White Brown	1T= 25g; 1SP= 60g; ½= 65g						
	Stamped wheat		1T= 30g; 1SP=80 g; ½c= 80g						
	Pasta	Macaroni	1T=						

		Spaghetti	35g; 1SP= 70g; ½c= 90g						
		Spaghetti & tomato sauce	1T= 45g; 1SP= 80g; ½c=125 g						
	Do you add fat to these starchy foods?	Yes No If yes, specify							
BREADS & SPREADS	Bread/ bread rolls	White	10mm= 30g; 20mm= 60g; 30mm= 400g; ½ loaf= 400g						
		Brown							
		Wholewheat	10mm= 35g						
		Other							
	Crackers	Provita	6g						
		Cream crackers	8g						
		Refined	4g						
		Wholewheat	8g						
	Are any of the following spreads on the child's bread?	Butter	1t= 5g						
		Lard							
		Hard margarine							
		Soft margarine (PM)							
		Soft margarine (Med)							
	Peanutbutter		1t= 12g						
	Sweet spreads	Jam	1t= 15g						
		Syrup							
		Honey							

	Marmite/ oxo		Thin= 2g; med= 4g; thick= 7g						
	Paste	Fish paste	Thin= 5g; med= 7g; thick= 10g						
		Meat paste							
	Cheese	Cheddar	Grated: med= 10g; thick= 15g; cube= 8g						
		Gouda							
		Cottage	Med= 20g; thick= 30g Thin= 10g						
		Cream cheese							
	Cheese spread		Med= 12g; thick= 25g						
	Atchar		1T=14g ; 1SP= 60g						
CHICKEN	Chicken	Boiled with skin	Breast= 125g Thigh= 80g Drumstick= 42g Foot= 30g Wing= 30g						
		Boiled without skin							
		Fried in batter/ crumbs							
		Fried, not coated							
		Grilled, with skin							
		Grilled, without skin							
	Chicken stew	With vegetables	1SP= 90g ½c=						

		With tom & onion	125g						
	Chicken offal	Giblets	Stomach= 20g						
	Chicken liver		Liver= 30g						
	Chicken pie	Comm./ homemade	Med= 150g						
RED MEAT	Beef	Roasted with fat	120x60x5=35g						
		Roasted, fat trimmed	120x60x10=70g						
		Rump, fried with fat	S/s 130x70x15=125g L/s 165x70x30=270g						
		Rump, fried without fat							
		Stewed with fat (vegetables)	1SP=105g; ½c=125g						
		Stewed without fat (vegetables)							
		Mince	1T=40g; 1SP=85g; ½c=100g						
	Mutton	Grilled, with fat	Loin chop=60g Rib chop=40g						
		Grilled, without fat							
		Stew	1SP=105g ½c=125						
		Stew, vegetable							
		Stew, curry							

		Stew, greenbean	g						
	Pork	Grilled, with fat	Chop:1 15x80x 20=100 g Roast:1 10x65x 5=30g 1SP=105g ½c=125g						
		Grilled, without fat							
		Roast, with fat							
		Roast, without fat							
MEAT: GENERAL	Offal	Liver:beef	80g						
		Liver: sheep	55g						
		Kidney: beef	85g						
		Kidney: sheep	30g						
		Tripe, beef	1SP=105g; ½c=125g						
		Heart, beef	60g						
		Heart, sheep	60g						
		Lung, beef	60g						
	Wors	Thin	200mm =45g						
		Thick	165mm =90g						
	Bacon	Fat	1 rasher= 10g						
		Lean							
	Cold meats	Polony	Sliced 5mm thick=8g; Comm slice=16g						

		Ham	Med slice=25g						
		Viennas	100mm =30g; 150mm =40g						
	Canned meat	Bully beef	138x85 x3= 20g; ½c=100 g						
		Other							
	Meat pie	Comm	120g						
	Legumes	Stews (Bean,potato & onion)	1T=60g ; 1SP=120g; ½c=125 g						
		Soups: Split pea Lentil Beef & vegetable Bean	½c=130 g; 1SP=80 g;1T=35g						
		Legume salad	1T=40g ; 1SP=105g; ½c=135 g						
	Soya products	Specify	1SP= 85g; ½c= 120g						
FISH	Fried fish	With batter	Small 50x55x 30mm= 60g Med 100x55 x30mm =120g						
		Without batter							
	Canned fish	Pilchards in tom sauce	1 pilchard = 75g						

		Pilchards, mashed	1SP=85 g; ½c=100 g						
		Sardines in oil	Small=7 g; Large= 25g						
		Sardines in tom sauce							
		Tuna in oil	½c=50g						
		Tuna in brine							
	Pickled/ curried fish		1SP=95 g; ½c=140 g						
	Fish cakes	Fried	65x15mm=50g						
	Fish fingers	Fried	85mm= 35g						
	Shellfish	Specify							
EGGS	Eggs	Fried	1 whole egg						
		Scrambled							
		Boiled							
CHEESE	Hard cheese		Grated: med 40g; 1 slice=8 g; cubes= 30g						
	Macaroni cheese		1T=45g ; 1SP=90 g; ½c=115 g						
	Cottage cheese; cream cheese								
VEGETABLES	Cabbage	Boiled	1T=30g ; 1SP=55 g; ½c=80g						
		Fried							

	Spinach/Marog	Boiled, nothing added	1T=40g ; 1SP=105g;½c=90g						
		Boiled with potato & onion	1T=50g ; 1SP=105g;½c=110g						
	Tomato & onion	Homemade	1T=35g ; 1SP=75g; ½c=140g						
		Canned							
	Pumpkin, specify type	Boiled	1T=45g ; 1SP=85g; ½c=105g						
		Cooked with fat & sugar							
	Carrots	Boiled, sugar & fat	1T=25g ; 1SP=50g; ½c=85g						
		With potato & onion	1T=35g ; 1SP=70g; ½c=105g						
		Raw, salad	1T=25g						
	Mealies	On cob	1T=30g ; 1SP=60g; ½c=95g						
		Creamed, sweet corn	1T=55g ; 1SP=125g; ½g=135g						
		Whole kernel corn							

	Beetroot	Cooked	1T=40g ; 1SP=70 g; ½c=80g						
		Salad	1T=25g ; 1SP=65 g						
	Potatoes	Boiled	Small=6 0g; med=90 g						
		Mashed	1T=50g ; 1SP=11 5g; ½c=125 g						
		Roasted	1 med=70 g						
		French fries	½c=50g ; med=80 g						
		Salad	1T=45g ; 1SP=10 5g; ½c=120 g						
	Sweet potato	Boiled	1T=50g ; 1SP=11 0g; ½c=145 g						
		Mashed							
	Green beans	Boiled	1T=30g ; 1SP=65 g; ½c=90g						
		Cooked, potato & onion	1T=40g ; 1SP=75 g; ½c=120 g						
	Peas	Cooked	½c=85g						

	Green pepper								
	Mushrooms		1T=30g; 1SP=65g; ½c=80g						
	Onions		1T=50g						
	Salad vegetables	Raw tomato	Med=120g; Slice=15g						
		Lettuce	1 leaf=30g						
		Cucumber	Medslice=10g; thick=15g						
		Avocado	¼avo (80x50 mm)=40g						
	Vegetable purees for babies or infants (specify)	First food vegetable (jar)	1t=5g; 1T=15g; ½c=47g						
		Junior food veg (jar)							
		Junior food veg plus meat							
		Other							
DRESSINGS	Mayonnaise/ salad dressing	Mayonnaise	1t=10g; 1T=40g						
		Salad dressing, French	1t=5g; 1T=15g						
		Oil	1t=5g; 1T=15g						
FRUIT	Apples		1 med=150g						
	Bananas		1 med=75g						
	Oranges/naartjies		Med=180g						

	Grapes		Med bunch= 230g; ½c=90g						
	Peaches		Med=150g						
	Apricots		Med=35 g						
	Mangoes		135mm = 350g						
	Pawpaw		Wedge 165x26 x27mm =90g						
	Pineapple		1 slice=40g						
	Guavas		Med=95 g						
	Pears		Med=165g						
	Dried fruit	Raisins	1 handful =27g						
		Prunes	1T=50g ; ½c=110 g; 1=12g						
		Peaches	Med=150g						
		Apples	1T=60g ; ½c=120 g						
		Dried fruit sweets							
	Fruit purees for babies/ infants	First food (jar)	Jar=200 g						
		Junior fruit (jar)	1t=11g ½c=125 g						
		Other							
DRINKS	Milk	Whole	½c=125 ml Baby bottle= 250ml						
		2%							
		Fat free							
		Sour							
		Infant formula, specify							

	Milk drinks	Drinking chocolate	1t=5g						
		Malted milk beverage	1t=5g						
		Flavoured milk	Carton=250ml; small plastic=350ml						
	Yoghurt	Drinking	Small=175ml; Yogisip=350ml; ½c=125g						
		Thick: fat free; Low fat							
	Squash (specify)		S/s glass=150ml; med=250ml large=500ml; small bottle=350ml, large=500ml; small can 350ml						
	Fruit juice	Specify							
	Fizzy drinks	Sweetened	S/s Bottle=350ml; L/s Bottle=500ml; s/s can=340ml						
		Diet							
SNACKS	Potato crisps								
	Peanuts								
	Cheese curls								
	Popcorn								
	Chocolates								
	Sweets	Specify							
	Biscuits/cookies	Specify							
	Cakes/tarts	Specify							
	Rusks								

	Scones		6cm diam=35g; 8cm diam=60g						
	Muffins								
	Koeksisters		100x35=60g						
	Savouries	Sausage rolls	135mm=165g						
		Samoosas	S/s=42g						
		Biscuits	4g						
PUDDINGS	Jelly		1T=35g; 1SP=75g; ½c=110g						
	Baked pudding	Specify	Med serv=30g; 30x65x65=50g						
	Instant pudding	Specify	1T=45g; 1SP=95g; ½c=145g						
	Infant desserts	Specify	Jar=200g; 1t=11g; ½c=125g						
	Ice cream	Specify	Scoop=40g; 1SP=65g; ½c=75g						
	Custard		1T=13g; 1SP=40g						

Are there any foods that the child eats which we haven't talked about?							
Foods	Description	Amount usually eaten	Times eaten				
			Per	Per	Per	Seldo	

			day	week	month	m	

Appendix 4: Immunologic categories for HIV-infected children based on age-specific CD4 T-lymphocyte count

Immunologic catagory	Cells/µl		
	<12 months	1-5 years	6-12 years
No evidence of suppression	≥1 500	≥1 000	≥500
Evidence of moderate suppression	750 – 1 499	500 - 999	200 - 499
Severe suppression	<750	<500	<200

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